

SCIENTIFIC AMERICAN

JULY 2000

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ALIEN CIVILIZATIONS

If they really exist,
why aren't they here?

DEADLY LAKES

Exclusive: Preventing
a catastrophe in Cameroon

THE WHY OF WEIGHT

CERN's new collider
seeks why matter has mass

SPECIAL REPORT

The Human GENOME BUSINESS

SPECIAL INDUSTRY REPORT

The Business of the Human Genome 48

The task of sequencing all human DNA is all but done, but mining the mountains of genetic information for pay dirt is just beginning. The new fields of bioinformatics and proteomics hold the keys to multibillion-dollar biotech industries of the future. Our reporters survey the science and look at the companies poised to cash in.

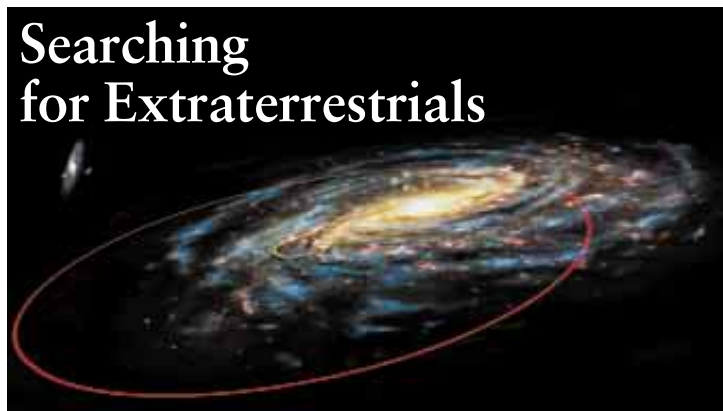


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Searching for Extraterrestrials



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Ian Crawford

Given how quickly (in cosmic terms) a galaxy can be colonized, an advanced alien civilization should by rights already be on our doorstep. Perhaps the human race is alone after all.

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Andrew J. LePage

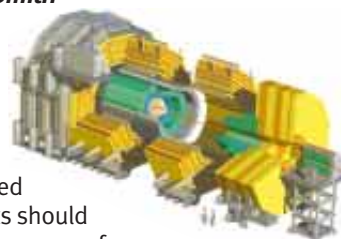
Radio scans seem to preclude the existence of a Galactic Empire. But civilizations more like our own could still be out there.

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Image by Jeff Johnson.

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EDITOR JOHN RENNIE

Bracing for the Imminent

A hundred years of warm-up should be enough; time to get to work. Exactly a century ago, in 1900, Hugo Marie de Vries, Carl Erich Correns and Erich Tschermak von Seysenegg independently rediscovered Gregor Mendel's 40-years-fallow work on the rules of heredity. About a decade passed before Thomas Hunt Morgan refined those ideas into a concept of heritable genetic units strung along the chromosomes. Francis Crick and James Watson's famous one-page paper proposed the double-helical structure for DNA in 1953, and that twisty key unlocked the secrets of the molecule. This year, in 2000, both Celera Genomics and the international government consortium of laboratories called the Human Genome Project are releasing complete drafts of the sequence of bases in human DNA—essentially, the unedited recipe books for every protein made by human cells.

That's an impressive gulf to have spanned in so short a time. But the view 100 years from now is even less conceivable, because the end of the genome projects marks only the beginning of biotechnology's ascent. Our examination of "The Business of the Human Genome," beginning on page 48, charts what to expect next. Just as computing evolved from a rarefied specialist's endeavor into a consumer pastime, genetic science is changing into a technology with everyday commercial applications. For some time to come, most of the products will be biopharmaceutical or diagnostic. Much further off is gene therapy, an attempt to redress disease at the level of DNA.

The new human genetic bonanza blends with similar gluts for other organisms, animal and vegetable. How today's biotechnology fares is likely to be instructive about how smoothly tomorrow's uses for the human genome will proceed. The agricultural industry, for example, is still wrestling with safety worries and intellectual-property-rights controversies over genetically modified crops. Watch for future articles and news stories in *Scientific American* for expert insights into these and similar issues as the human genetic information goes to market.

Modern technology is a poor shield against most natural disasters. Prediction is often all that science can offer, with an eye toward evacuating regions where hurricanes, tornadoes or earthquakes are about to occur. Prevention—the ability to stop a force of nature before it can kill—usually eludes us.

But a repeat of the lethal release of natural carbon dioxide from lakes in Cameroon that suffocated hundreds in the 1980s is entirely preventable, as contributing editor Marguerite Holloway describes in "The Killing Lakes," beginning on page 92. She was the only reporter on the scene when researchers recently returned in preparation for the degassing project. An inexpensive means of safely venting the gas exists. The catch is that aid organizations are accustomed to picking up the pieces after a disaster, not heading one off. Again: let's get to work *now*.



Like computing, genetic science is evolving into a consumer technology.

John Rennie
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HUMAN MISSION TO MARS

Glenn Zorpette's article "Why Go to Mars?" mentioned science and nationalism, but there are more fundamental reasons for Mars missions: economic growth, which will open up the vast material and energy resources of the solar system; security for our civilization against global disasters; and the redefinition of what it means to be human—beyond the old paradigms of the cruel destroyer or the mindless consumer toward a consciousness of humankind as an agent of creation, spreading life from one world to many. Mars exploration should be thought of not as a heroic adventure isolated from other human concerns but rather as part of the organic evolution of society and of terrestrial life.

STEPHEN ASHWORTH
Oxford, England

I found the special report "Sending Astronauts to Mars" very stimulating, but in Robert Zubrin's "The Mars Direct Plan," some of the projected methods seemed a bit too accommodating to political interests. For hundreds of thousands of years, humans have used available materials to construct camps, settlements, whatever they needed when establishing a presence in a new territory. Must one really offer plans that will create lucrative contracts? At the most fundamental level, surely simple machines such as levers that could be used to pile up suitable boulders and rocks into walls, coupled with imperme-

able films, expandable foams and support beams (granted, not available on Mars), would be cheaper and easier to transport than an entire habitat (or series of habitats) and would establish a much more permanent base of operations.

DAVID LAURENCE
via e-mail

I read with great interest "Staying Sane in Space," by Sarah Simpson. Astronauts have traditionally been chosen from the ranks of test pilots, people with highly trained minds and bodies. Unfortunately, such a body rapidly deteriorates during a long period of inactivity, and a mind trained to make split-second life-or-death decisions is not likely to be content spending years with a small group confined in space. A body that was never very fit is not likely to change much in a small spaceship, and the world abounds with people content to spend all of their waking hours in front of a TV or computer screen. The solar system will not be successfully explored by people with "the Right Stuff." It will be conquered by couch potatoes.

LEO A. FRANKOWSKI
via e-mail

SHOTS IN THE DARK?

With regard to "Granting Immunity," by Sasha Nemecek [News and Analysis], I would like to point out that vaccines are preserved with thimerosal, a mercury-based preservative. Mercury is a well-known toxic substance. Most vaccine



HUMANS ON MARS could look for life.

makers now warn that anyone allergic or highly reactive to thimerosal should not be given the vaccine. About 10 percent of the population reacts in this way, and the consequences can be severe, which means that the health of millions of babies and children worldwide is being compromised.

ROSEMARY CARTER
Crescent Valley, B.C.

The benefits of the various vaccines are obvious, but one wonders about the possible hazards of overloading an infant's immune system with 10 injections before her first birthday. Is it necessary to administer them so early, or is it done simply because physicians have frequent access to children in their first year? Fatherhood has not made me so overprotective that I doubt modern medicine, but the speed with which we add new vaccines to the repertoire and the immensity of the implied profits for the vaccine producers do make me wish for more thorough answers to these difficult questions.

JIM DAWSON
via e-mail

Nemecek replies:

Carter is correct that thimerosal, which contains the compound ethyl mercury, is used to prevent bacterial contamination in many vaccines. Anyone with a known sensitivity to thimerosal should avoid it (just as people who are allergic to eggs should skip the influenza vaccine, which contains traces of egg). But according to the Centers for Disease Control and Prevention, thimerosal has not proved harmful after more than 50 years of use in vaccines. In an effort to minimize the public's exposure to mercury, however, the U.S. Public Health Service, the American Academy of Pediatrics and drug companies are working to eliminate thimerosal from vaccines. In August 1999 the U.S. Food and Drug Administration licensed a thimerosal-free hepatitis B vaccine, which is gradu-

THE MAIL

READERS had no shortage of opinions regarding the articles in our March issue's special report "Sending Astronauts to Mars." Some were enthusiastic about the prospect, whereas others, such as Philip E. J. Green of Mississauga, Ontario, wondered whether the funding required for such a mission might be better dedicated to life on our own planet. "Your March issue is a tragically ironic snapshot of the state of science today," Green writes. "Seven articles are devoted to a multibillion-dollar expedition to Mars, the main goal of which is to look for life. One article describes scientists who scramble up cliffs and trees to collect samples of bromeliads in the Mata Atlantica before they are wiped from the face of the earth. In the face of massive and rapid loss of life-forms on this planet," he states, "I propose canceling any plans to send people to Mars and diverting 10 percent of the Mars budget to finding and preserving life on Earth." Additional comments about the Mars report and other articles in the March issue are featured above.



ally becoming available across the country.

Dawson's concerns are shared by many parents, and in some cases, the vaccine schedule can be modified. Parents worried about thimerosal in the hepatitis B vaccine, for instance, can ask about postponing the first dose until their baby is between two and six months. Dawson's hunch about the importance of frequent visits to the doctor in a child's first year is accurate: research has found that delaying vaccines very often results in incomplete inoculation.

EXPLAINING ETHER

In his commentary "Wuff, Wuff," James Burke implies that nitrous oxide and diethyl ether are the same. Although nitrous oxide is still in common use as a general anesthetic, its initial public demonstration by Horace Wells—in the operating room that later came to be known as the Ether Dome—was a failure. The following year (1846), another substance, ether (now essentially abandoned as an anesthetic), was used in the first successful public demonstration of inhalation anesthesia by William Morton at Massachusetts General Hospital.

SETH A. WALDMAN
Department of Anesthesiology
Weill College of Medicine
Cornell University

Burke replies:

I apologize for the error. Confusion arose because the term "ether" was often used indiscriminately at the time for any respirable "air" or fluid such as nitrous oxide, ether proper or chloroform.

Letters to the editors should be sent by e-mail to editors@sciam.com or by post to Scientific American, 415 Madison Ave., New York, NY 10017. Letters may be edited for length and clarity. Because of the considerable volume of mail received, we cannot answer all correspondence.

ERRATUM

Because of a printing error in the April issue, a line was lost from "Power to the PC" [News and Analysis]. The sentences between pages 27 and 28 should have read: "... his more robust Cosm system is more in line with the field's 30-year history than are the examples of 'collaborative computing' currently on-line. Cosm's platform-independent software will run on any computer..."

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Smoking and Cancer, Pioneers of Flight (or Fright)

JULY 1950

LANDMARK TOBACCO REPORT—"Tobacco has often been suspected of complicity in the great increase in lung cancer since 1900. But the evidence has been fragmentary and conflicting. A well-documented report in the *Journal of the American Medical Association* presents what appears to be the strongest evidence thus far that smoking may cause cancer. Ernest L. Wynder and Evarts A. Graham of the Washington University School of Medicine found in a national survey that among 605 men with cancer of the lung, 96.5 per cent had smoked at least 10 cigarettes a day for many years; whereas in the general male hospital population without cancer only 73.7 per cent were regular smokers."

PLUTO—"The outermost planet of the solar system has a mass 10 times smaller than hitherto supposed, according to measurements made by Gerard P. Kuiper of Yerkes Observatory, using the 200-inch telescope on Palomar Mountain. On the basis of deviations in the path of the planet Neptune, supposedly caused by Pluto's gravitational attraction, it used to be estimated that Pluto's mass was approximately that of the earth. Kuiper was the first human being to see the planet as anything more than a pinpoint of light. He calculated that Pluto's diameter is 3,600 miles, and its mass is one tenth of the earth's. It leaves unsolved the mystery

of Neptune's perturbations, which are too great to be accounted for by so small a planet as Pluto."

GREED—"Is avarice a natural tendency or an acquired habit? Harvard psychologists Louise C. Licklider and J.C.R. Licklider provided six rats with all the pellets of Purina Laboratory Chow they could eat. Although none of the rats had ever experienced a food shortage, all immediately started hoarding pellets. The Lickliders refined the experiment: they covered half of the pellets with aluminum foil, thus eliminating their value as food. They discovered that four of the six avaricious rats actually preferred the worthless, inedible pellets in hoarding."

JULY 1900

PIONEER AERONAUT—"M. de Santos Dumont [sic] recently finished the new air ship with which he is to compete for the Aero Club's Deutsch prize for the first flight from the Bois de Boulogne around the Eiffel Tower. The aeronaut and propelling mechanism are suspended from the gas-filled envelope [see illustration below]. The gasoline motor is started by means of a pedal and chain gear. The upper cylinder contains gasoline for the motor, and in the lower is a reservoir of water which is used as ballast." [Editors' note: *The Brazilian-born Alberto Santos-Dumont won the Deutsch Prize on October 19, 1901.*]

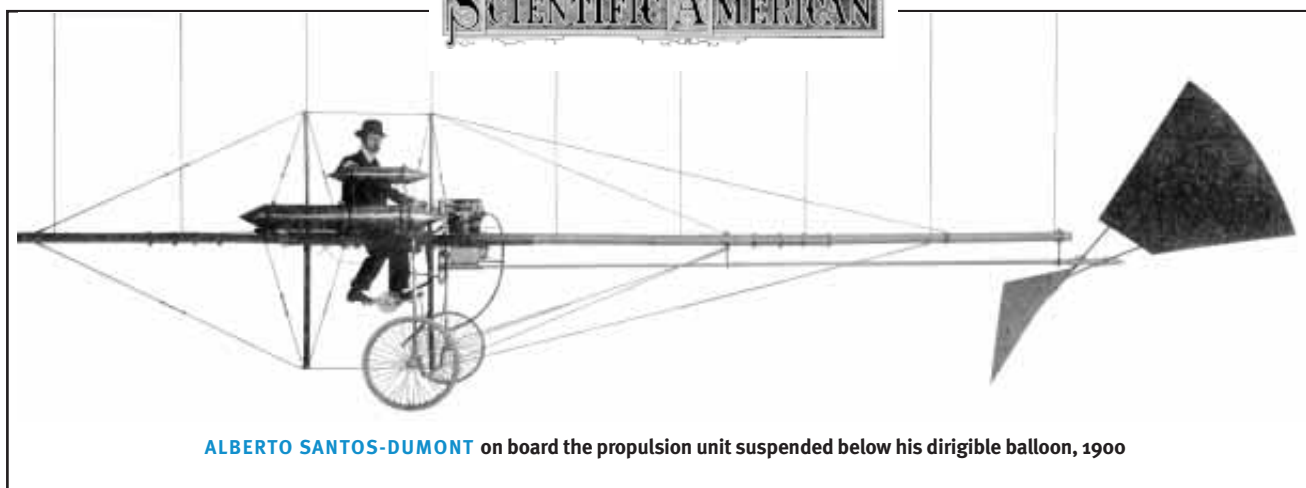
JULY 1850

THE IMPROBABLE PHINEAS GAGE—"Prof. Bigelow, of Harvard University, brings us the latest on a young man named Phineas P. Gage, who had a huge iron rod shot through his brain in September, 1848, and strange to say he is now *living* and in general health. 'The leading feature of this case,' says Prof. Bigelow, 'is its improbability.' Prof. B. says that he was 'at first wholly skeptical,' but that he was personally convinced. Mr. Gage visited Boston in January, and was for some time under the professor's observation, who had his head shaved and a cast taken; which, with the tamping iron, is now deposited in the Museum College."

NATURE'S NEW COURSE—"It is but a little more than twenty years since the first crow crossed the Genesee River westwardly. The crow, the fox, the henhawk, swallow, and other birds and insects seem to follow civilization. The grain weevil began its course of destruction in Vermont, about the year 1828, and it progresses from ten to fifteen miles a year. It has not yet reached Western New York; but the destroyer is on its march, and desolation will follow in the wheat-growing region."

FEAR OF FLYING—"A French lady, who had ascended in a balloon from Lisbon, was about to descend at a village near the Tagus, but the villagers, mistaking her for a witch, crossed themselves, and loudly proclaimed their defiance of the devil and all his works; some ran away; others fell on their knees and roared for mercy; while a few prepared their weapons for an assault. The poor lady threw out ballast and re-ascended, and landed, unaided, in safety at another spot."

SCIENTIFIC AMERICAN



ALBERTO SANTOS-DUMONT on board the propulsion unit suspended below his dirigible balloon, 1900

Boomerang Effect

Balloon data confirm the big bang—and challenge it, too

Usually cosmology goes like this: new observations come in, scientists are baffled, models are upended. After the dust settles, however, patches are affixed and the prevailing theory emerges largely intact. But when the measurements by the Boomerang and Maxima telescopes came in, the sequence was reversed. Scientists were elated. "The Boomerang results fit the new cosmology like a glove," Michael S. Turner of the University of Chicago told a press conference in April. And then the dust settled, revealing that two pillars of big bang theory were squarely in conflict—a turn of events that could be nearly as monumental as the discovery of cosmic acceleration just over two years ago.

Both telescopes observed the cosmic microwave background radiation, the remnant glow of the big bang. Boomerang, lofted by balloon in December 1998 for 10 days over Antarctica, had the greater coverage—3 percent of the sky. Maxima, which flew above Texas for a night in August 1998, scrutinized a tenth the area but with higher resolution. The two instruments made the most precise maps yet of the glow on scales finer than about one degree, which corresponds to the size of the observable universe at the time the radiation is thought to have been released (about 300,000 years after the bang). On this scale and smaller, gravity and other forces would have had enough time to sculpt matter.

For those first 300,000 years, the photons of the background radiation were bound up in a broiling plasma. Because of random fluctuations generated by cosmic inflation in the first split second, some regions happened to be denser. Their gravity sucked in material, whereupon the pressure imparted by the photons pushed that material apart again. The ensuing battle between pressure and inertia caused the plasma to oscillate between compression and rarefaction—vibrations characteristic of sound waves. As the universe aged, coherent oscillations devel-

oped on ever larger scales, filling the heavens with a deepening roar. But when the plasma cooled and condensed into hydrogen gas, the photons went their separate ways, and the universe abruptly went silent. The fine detail in the background radiation is a snapshot of the sound waves at this instant. Areas of compression were slightly hotter, hence brighter; areas of rarefaction, cooler and darker.

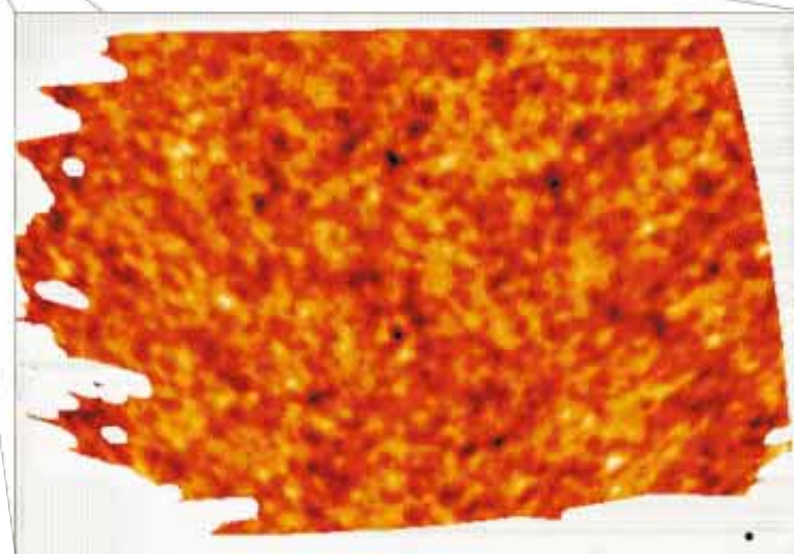
From the Boomerang and Maxima data, cosmologists expected a profusion of large spots (oscillations that had most recently begun), spots half that size (oscillations that had gone on for longer), spots a third the size (longer still), and so on. On either a Fourier analysis or a histogram of spot sizes, this distribution would show up as a series of peaks, each of which corresponds to the spots of a given size [see illustration on opposite page]. The height of the peaks represents the minimum amount of compression (odd-

numbered peaks) or of rarefaction (even-numbered peaks) in initially dense regions. Lo and behold, both telescopes saw the first peak—which not only confirms that sounds reverberated through the early universe, as the big bang theory predicts, but also shows that the sounds were generated from preexisting fluctuations, as only inflation can produce.

The next implication is for the geometry of the universe. If the rules of Euclidean trigonometry apply (as they do on a flat sheet of paper), the dominant spots should subtend 0.8 degree after accounting for cosmic expansion. If space is instead curved like a sphere, the spots will look larger; if it is curved like a saddle, they will look smaller.

Boomerang measured an angle of 0.9 degree—close enough for the team, led by Paolo de Bernardis of the University of Rome and Andrew E. Lange of the California Institute of Technology, to declare

NO ONE CAN HEAR YOU SCREAM in space today, but the primordial universe was dense enough to transmit sounds—which show up as temperature variations in detailed views of the cosmic background radiation.



Temperature Deviation from Average (microkelvins)

in *Nature* that space is Euclidean. The Maxima team, in papers by Amadeo Balbi of Rome and Shaul Hanany of the University of Minnesota, reached the same conclusion, as did results from earlier telescopes, albeit with less precision. Yet follow-up studies soon showed that the lingering discrepancy, taken at face value, indicates that the universe is in fact spherical, with a density 10 percent greater than that required to make it flat. Such a gentle curvature seems awkward. Gravity quickly amplifies any deviations from exact flatness, so a slight sphericity today could only have arisen if the early universe was infinitesimally close to flat. Modified versions of inflation might explain this fine-tuning, but most cosmologists regard them as last resorts.

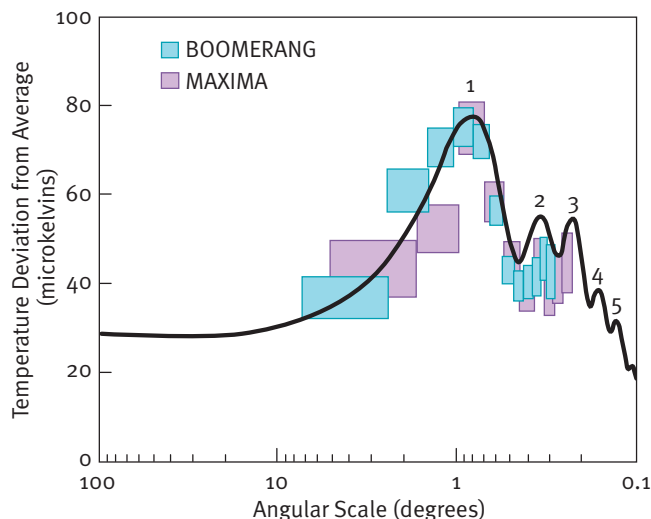
A more palatable alternative is that the trigonometric calculation somehow did not properly account for cosmic expansion. This would happen if the radiation did not travel as far as assumed—that is, if it was released later in cosmic history, if the famous Hubble constant were larger (making the universe younger), if the universe contained more matter (holding back the expansion) or if the cosmological constant were smaller (taming cosmic acceleration). All these possibilities, however, seem to contradict other observa-

tions. A way to keep the peace is if the cosmological constant has not, in fact, been constant. Its inconstant cousin, known as quintessence, would impart a milder acceleration. As Paul J. Steinhardt of Princeton University has argued, quintessence would also explain why the first peak is lower than it should be. Something seems to have monkeyed with the radiation since its release, and quintessence would indirectly do exactly that.

The second big mystery in the data is even more dire: there is only the merest hint of a bulge where the second peak should be. That suggests that the primordial plasma contained surprisingly many

subatomic particles, which would weigh down the rarefaction of the sound waves and thereby suppress the even-numbered peaks. But accounting for those extra particles is no easy matter. According to Max Tegmark of the University of Pennsylvania and Matias Zaldarriaga of the Institute for Advanced Study in Princeton, N.J., the Boomerang results imply that subatomic particles account for 50 percent more mass than standard big bang theory predicts—a difference 23 times larger than the error bars of the theory. “There are no known ways to reconcile these measurements and predictions,” says nucleosynthesis expert David R. Tytler of the University of California at San Diego. One mooted solution, a steeply “tilted” version of inflation that did not create fluctuations uniformly on all scales, also contradicts the data.

New information due out soon could resolve some of the problems: only part of the Boomerang and Maxima data has been analyzed, and both balloons will fly again this year in search of the decisive third peak, an inkling of which appeared in the Maxima observations. Several other experiments are planned, and the long-awaited Microwave Anisotropy Probe is now scheduled to launch next spring. That roar in the heavens may have been laughter at our cosmic confusion. —George Musser



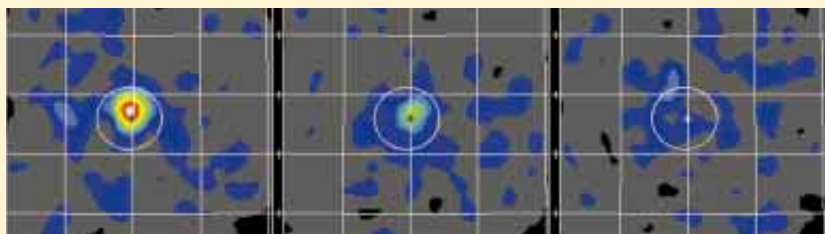
COSMIC MISMATCH: Fourier analysis of the spots seen by Boomerang and Maxima differs subtly but significantly from the predicted multip peaked curve (black), shown here to the fifth peak.

Gamma-Ray Candles

Nature's brightest objects make for convenient cosmic yardsticks

To determine the basic properties of the universe, cosmologists combine results such as Boomerang's with measurements of cosmic expansion and distance, which rely on type Ia supernovae and other celestial bodies of known brightness. Now researchers have a new standard candle: gamma-ray bursts. Edward E. Fenimore of Los Alamos National Laboratory and Enrico Ramirez-Ruiz of the University of Cambridge have found that the more rapidly flickering a burst is, the brighter it shines. Although this correlation pins down brightness to within only a factor

of five—compared with the 20 percent precision for supernovae—the bursts are visible billions of light-years farther away. In a paper submitted to the *Astrophysical Journal*, the researchers gauge the distance to 224 bursts and conclude that star formation was far more intense in the early universe than has been thought. From this they hope to work out the effects of dust and thereby refine supernova measurements of cosmic acceleration. Explaining why bursts follow such a rule may also shed light on their enigmatic origins. —G.M.



GAMMA-RAY BURST of December 14, 1997, seen here fading away in x-rays, is one of 20 bursts of known distance. Their properties establish a pattern that allows the distances of other bursts to be estimated indirectly.

AGE Breakers

Rupturing the body's sugar-protein bonds might turn back the clock

LONDON—For all the promise of anti-aging creams and therapies, nothing has ever restored the vigor of youth or even delayed the inevitable process of growing old. Researchers now claim to have developed a compound that might rejuvenate hearts and muscles—by breaking the stiff sugar-protein bonds that accumulate as we get older.

Anthony Cerami of the Kenneth S. Warren Laboratories in Tarrytown, N.Y., suspected some 30 years ago that sugar affects how the body ages, based on observations of diabetics, who age rapidly. Sugars are an essential source of energy, but once in circulation they can act as molecular glue, attaching themselves to the amino groups in tissue proteins and cross-linking them into hard yellow-brown compounds known as advanced glycation end products, or AGEs.

Indeed, after years of bread, noodles and cakes, human tissues inevitably become rigid and yellow with pigmented AGE deposits. For the most part, piling on dark pigments in the teeth, bones and skin is harmless. But where glucose forms tight bonds with the long-lived protein collagen, the result is a constellation of changes, including thickened arteries, stiff joints, feeble muscles and failing organs—the hallmarks of a frail old age. (Diabetics age prematurely because sugar-driven damage acquires breakneck speed, raising their levels of AGE-infused collagen to those of elderly people.) “The evidence that sugar cross-linking increases as we age is persuasive,” comments Jerry W. Shay of the University of Texas Southwestern Medical Center at Dallas. “There are diseases associated with increased glycation, which are directly related to increased age.” Sugar’s connection with AGE formation may be one reason caloric restriction might delay aging.

Cerami’s quest has been to find an “in-

hibitor”—a compound that by tying up reactive glucose might keep it away from susceptible proteins. To his surprise, the food industry had the answer. Since 1912 chemists have known that in the heat of an oven sugars and amino acids form tight chemical bonds—a reaction that turns roasted turkey, toast and coffee to a tasty golden brown. This Maillard chemistry, as it is known in food circles, is the



FOOD FOR THOUGHT: A roasted turkey may hold the clues to reversing aging.

same sugar-protein bonding that stiffens our tissues. Crucially, food chemists also discovered that adding sulfites prevents browning and hardening and keeps food and beverages looking fresh.

Exploiting this culinary knowledge, Cerami’s team showed in the mid-1980s that aminoguanidine could keep the tissues of diabetic rats and other old animals as elastic as those of young control subjects. It boosted their cardiovascular function and improved other age-related disorders. Further studies showed that aminoguanidine lowered diabetics’ urine albumin—an indicator of kidney malfunction—and delayed AGE-related damage to the retina.

Perhaps more exciting is Cerami’s re-

cent discovery of a molecular “breaker”—a drug that may actually reverse the aging process by cracking sugar-protein links once they form. “Instead of looking for prevention, we can now administer a compound to reduce the stiffness we see in diabetes and aging,” Cerami reported at a recent Novartis Foundation symposium in London. The breaker, dimethyl-3-phenacylthiazolium chloride, or ALT-711, can tear tough AGE bonds apart. Diabetic animals, old dogs and elderly rhesus monkeys given the compound daily for three weeks yielded spectacular results. “The heart and major arteries, which were quite stiff, became more pliable and elastic. So the heart could pump more blood—similar to what you’d see in a young animal,” Cerami stated.

Cerami envisages multiple uses for breakers in pathologies wherein tissues lose flexibility. In glaucoma, for example, increasing the elasticity of the draining canal would prevent the buildup of pressure in the eye. ALT-711 could also renew declining lung elasticity and soften an enlarged and hardened prostate. But it will be at least 10 years until such drugs, currently undergoing clinical trials, are approved for humans.

Will breakers stop aging in its tracks? After all, the field of antiaging drugs is littered with compounds that failed to live up to their hype or were hardly more than snake oil [see *SCIENTIFIC AMERICAN PRESENTS: The Quest to Beat Aging*; Summer 2000]. A single fountain-of-youth elixir is highly unlikely, says Tamara Harris of the National Institute on Aging, because other activities, such as free-radical oxidation and possibly telomere shortening, also contribute to the body’s slow decline. Moreover, AGE-related research tends to be slow: Harris points out that there is no easy, well-validated way to measure AGE in the body, a shortcoming that complicates trials. To Harris, however, AGE breakers remain an appealing option. “This is a nice approach because it is multifocal, aimed at a basic process that occurs in multiple systems. But,” she warns, “there won’t be one silver bullet.”

—Lisa Melton

LISA MELTON, who has a Ph.D. in immunology, is a science writer and television researcher based in London. She has an unfortunate penchant for cake.

DEFENSE TECHNOLOGY COMMUNICATIONS

Reengineering the Radio

The Pentagon and industry plan for software-based transceivers that combine voice, video and data

WASHINGTON, D.C.—In August 1998 the Pentagon leadership put the word out to U.S. military services that purchases of new battlefield radios, with very few exceptions, had to be stopped: the military was newly committed to an innovative family of radios, and anything that didn't fit within the new regime had to go. Now, two years later, the program is due to command at least half a billion dollars in the Pentagon's budget over the next few years, and the radios are slated for use not just in military platforms but also for the Federal Aviation Administration and other government agencies, including local police and fire departments. The commercial market is also expected to be substantial, reaching into the billions of dollars.

This will be no ordinary radio. Rather than simply transmitting voice, the Joint

trucks and soldiers will have versions tailored to their needs.

By building to a common standard and "migrating" existing systems to that standard, the Pentagon hopes to ensure that all forces at all levels can communicate during wartime, which they can't always do today. "It's going to completely redo the way that [military] people will use communications devices in the future," remarks deputy program manager Col. Michael C. Cox. Optimistically, the first radios could be in use in two years, after which as many as 750,000 radios could be replaced within only 10 years—an extraordinary schedule for the Pentagon, an institution that has never enjoyed stable funding.

Cox describes JTRS more as a process than as a traditional military program. His office, he explains, has served as a "catalyst" to commercial cooperation, driving "previously antagonistic" companies to collaborate on a common, open architecture. "There are proprietary software radios out there today," he notes, "but they're not compatible" with one another. Raytheon, Motorola and Boeing are major players, although virtually every radio manufacturer has an interest.

Not everyone is happy with JTRS, though. According to the Defense Science Board, a

group of influential advisers to the U.S. defense secretary, JTRS isn't the revolutionary leap forward the military needs. In a February report the board singled out JTRS as one of the most egregious examples of a flawed Pentagon communications improvement strategy. The "potential impact" of JTRS, the advisers said, is "clearly under appreciated."

JTRS could be the foundation of a Pentagon-wide intranet the panel believes is sorely needed. The networking aspects of

JTRS, however, have been "lost" amid plans to move existing systems to a common architecture, the report stated, and the push for consensus among industry and the military is "driving the program to focus on the past."

Cox concedes that in a perfect world the Pentagon would replace all radios in use today with ones that seamlessly connect everyone in a state-of-the-art network, thereby satisfying the science board. But, he says, cost and other factors make this a pipe dream. Better to develop a system that works with existing radios but provides significantly improved communications and the ability to upgrade radios with new technology.

In any case, the radio system's potential is huge, supporters insist. Beyond the military, fire and police departments and other emergency-response agencies have been eyeing it. Many ambulances, Cox points out, must carry as many as seven radios, which together can cost more than the ambulance itself. An open-standard radio could solve this problem, allowing emergency-response workers of all stripes to talk to one another. "Why can't we talk when lives are at stake?" he asks. "This is a radio that would provide that interoperability."

First, JTRS must be the boon to the military that the Pentagon claims it will be. JTRS is a program driven to an uncommon degree by the civilian defense leadership and not the services themselves, and such arrangements do not always run smoothly. Overall, according to the Defense Science Board, military communications funding is inadequate for current and future requirements. But if industry can be driven to work together on a common architecture that meets everyone's needs, "then everyone can build to it," and Cox concludes, "everybody wins."

—Daniel G. Dupont

DANIEL G. DUPONT is editor of the newsletter *Inside the Pentagon in Washington, D.C.* He described military image-recognition technology research in the December 1999 issue.



BATTLEFIELD RADIOS may become obsolete if software-programmable units take over.

Tactical Radio System (JTRS), as the Pentagon refers to it, will also simultaneously carry video and data transmissions. It will be the military's first widely used software-based radio, relying on a computer to generate multiple waveforms between five and 2,000 megahertz. The software will be based on a wholly "open" architecture, in which the operating system is made publicly available, although it will have security features such as encryption. Jets, helicopters, tanks,

ASTRONOMY GEOMAGNETIC STORMS

Fire in the Sky

Space weather turns gusty as solar activity approaches its peak

On April 6 the Advanced Composition Explorer spacecraft, located about 1.5 million kilometers from the earth, detected a huge surge in the solar wind, the stream of ions and electrons emanating from the sun. Forty minutes later the interplanetary shock wave slammed into the earth's magnetic field, triggering the biggest geomagnetic storm in nearly a decade. High-energy particles raced along field lines toward the planet's magnetic poles; as they struck the nitrogen and oxygen molecules in the upper atmosphere, they produced brilliant green and red auroras. Such displays are typically visible only at high latitudes, but the auroras on that evening were observed as far south as Florida and Texas.

If you missed the fireworks, don't worry. The scientists who study space weather say solar storms will continue to buffet the earth for the next two years or so. The sun's turbulence waxes and wanes on an 11-year cycle, and the period of peak activity—the solar maximum—has just begun. Judging by the number of sunspots (a rough indicator of solar agitation), the current maximum will be livelier than most, though not quite as violent as the

1989–1991 maximum. (A space storm in March 1989 knocked out a power grid in Quebec, depriving six million people of electricity.) Researchers are eagerly awaiting the stormy season, because for the first time they can use space observatories to track the progress of the tempests and perhaps learn how to forecast them. “We’re blessed with lots of good observations,” says David Hathaway, a solar physicist at the National Aeronautics and Space Administration Marshall Space Flight Center in Huntsville, Ala. “But we don’t yet have a good theory to put the whole picture together.”

The fiercest solar upheavals fall into two categories: flares and coronal mass ejections. A solar flare is a brief, intense burst of radiation that occurs on the sun's surface, usually near sunspots. A coronal mass ejection (CME), in contrast, is an eruption in the sun's outer atmosphere that hurls billions of tons of material into interplanetary space at speeds as high as 2,000 kilometers per second. Physicists theorize that fluctuations in the sun's magnetic field cause sunspots, flares and CMEs, but they have no idea why the upheavals follow an 11-year cycle. Recent data from the Solar and Heliospheric Ob-

servatory (SOHO), which has been orbiting the sun since 1995, show some periodic variation in the rotation rate of the layer of the sun's interior where the magnetic field is thought to be generated. But this variation may be a consequence of the solar cycle rather than its cause.

Scientists used to think that solar flares triggered geomagnetic storms, but now they believe the chief culprits are the interplanetary shock waves produced by CMEs. (Two days before the April 6 storm, SOHO detected a powerful CME pointed directly at the earth.) When a strong shock wave hits the earth's magnetic field, it can tangle the field lines; this disruption accelerates the charged particles trapped in the field, driving them into our planet's atmosphere. Some storms last only a few hours, but others go on for days. Over the years the disturbances have fried the electronics of a dozen communications and weather satellites.

To allow researchers to study the phenomenon, NASA recently launched the Imager for Magnetopause-to-Aurora Global Exploration (IMAGE), a satellite that will be able to monitor the particle flows during geomagnetic storms and observe the resulting auroras. “We just missed the April 6 storm,” says Jim Burch, IMAGE's principal investigator. “But it's a two-year mission, and there will be more storms of that magnitude.”

If space weather forecasters could provide timely warnings of storms, telecommunications companies could take steps to protect their satellites. The key to long-range forecasting will be tracking the active regions of the sun where flares and CMEs are most likely to erupt. Solar physicists have already devised two ingenious methods for detecting active regions when they are on the sun's far side (the sun rotates every 27 days). One method measures vibrations of the sun's surface caused by sound waves bouncing inside the gaseous body; the pattern can reveal magnetic activity on the far side. The other monitors the illumination of hydrogen atoms in the outer solar system using radiation from the sun's active regions, which act much like spotlights.

These techniques could give warnings of potential storms a couple of weeks before the choppy weather hits the earth. “We definitely need to improve our forecasting,” says Gary Heckman, senior forecaster at the Space Environment Center run by the National Oceanic and Atmospheric Administration. “We’re about 50 years behind the meteorologists.” —Mark Alpert



NORTHERN LIGHTS, as seen from Prince Edward Island, Canada, shimmered in the sky on April 6 after a shock wave from the sun hit the earth's magnetic field.

The Geography of Death

The maps summarize information on more than 9.3 million white Americans whose deaths were recorded from 1988 to 1992. According to the National Center for Health Statistics, the deaths resulted from more than 2,000 causes, including AIDS, pneumonia, accidents and homicide. But the patterns on the maps show, more than anything else, the impact of the three most common causes: coronary heart disease, stroke and lung cancer, which together constitute 35 percent of all deaths in the U.S. (Mortality rates for blacks follow a somewhat similar geographical pattern.)

The three leading diseases, which tend to be concentrated in the Southeast, are responsible for much of the higher mortality in that region, where two major risk factors—cigarette smoking and hypertension—are prevalent. Women in some areas of the West began smoking before women in most other areas, hence the high mortality rates there. The low mortality rates in Utah trace to the Mormons; the low rates in the Dakotas, Minnesota and Wisconsin trace to the Lutherans. Both groups typically practice a conservative lifestyle, including avoidance of smoking and other self-destructive behaviors. The low rates in Florida reflect the migration of retirees from the North, who tend, as a group, to be healthier than those remaining behind.

Recently epidemiologists have gone beyond risk factors and focused on poverty and poor education as explanations for excess mortality: less well off Americans often adopt unhealthy habits. Low socioeconomic status by itself, however, is not a satisfactory reason. It does not, for example, account for the

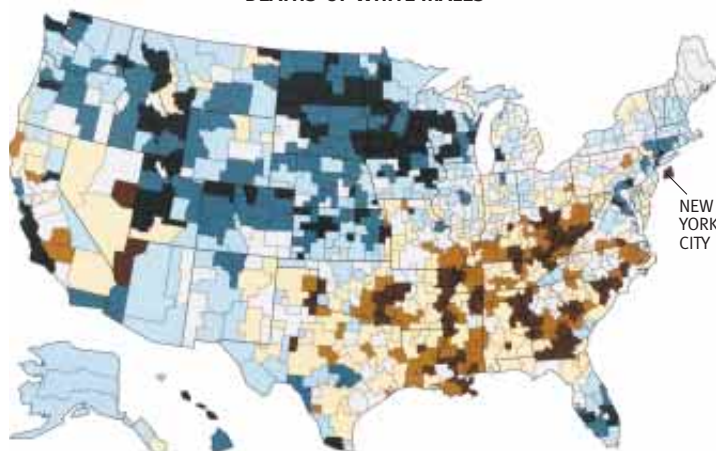
fairly low mortality among Mexican-Americans, who have high poverty rates. A better explanation may lie in the distribution of income. States with significant income inequality also tend to have high mortality rates, a relation that holds for both whites and blacks. Southern states generally have greater income inequality, whereas Utah, the Dakotas, Minnesota and Wisconsin tend to have less.

Unequal income distribution may shorten lives because it degrades civic cohesion. Ichiro Kawachi and his colleagues at the Harvard University School of Public Health measured civic cohesion in terms of participation in community groups and by the extent to which people trust one another, as measured by such statements as "Most people would try to take advantage of you if they got the chance." They found that in states with high mortality, such as those of the Southeast, trust in others is low and that in states with low mortality, such as Minnesota, North Dakota and Utah, trust is high.

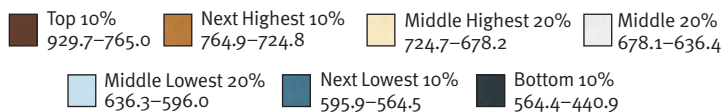
As for public policy, Kawachi believes that reducing income inequality would help lower mortality; he suggests prescriptions that might include raising the minimum wage, expanding the earned income tax credit and increasing child care subsidies. Others, such as Harvard researcher Christopher J. L. Murray, hold that the best approach is to rely on public health measures. Because research on this subject is not an exact science, there is likely to be considerable room for continued disagreement.

—Rodger Doyle (rdoyl2@aol.com)

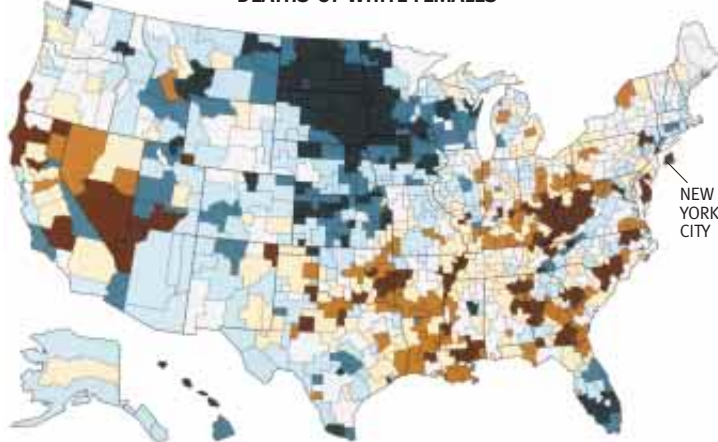
DEATHS OF WHITE MALES



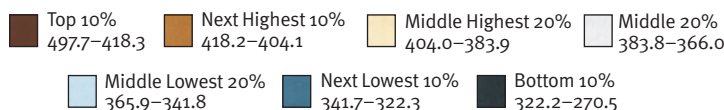
Age-adjusted mortality per 100,000 population



DEATHS OF WHITE FEMALES



Age-adjusted mortality per 100,000 population



SOURCE FOR MAPS: Atlas of United States Mortality, National Center for Health Statistics, Washington, D.C., 1996. The data, which are for 1988–92, are plotted for each of 805 health service areas, as defined by the U.S. Department of Health and Human Services. Deaths are from all causes.

Diseased Passage

Crossing the sewage-filled New River, migrants risk their health—and others'

CALEXICO, CALIF.—We've been camped out on a rickety bridge since morning, and after 11 hours we have almost had it. The bridge spans a river that collects dead farm animals, tires, floating sewage and industrial waste. Desert breezes in this permanently dusty agricultural region waft choking odors across a nearby grocery store parking lot, making the idea of food unappealing.

About an hour after sunset, our patience is rewarded: my photographer and I see 10 nearly naked immigrants come through a 20-foot-high corrugated-steel fence and wade into the New River, each clutching a sack of belongings in one hand and an inflated inner tube in the other. "Aren't you afraid of the water?" I yell in Spanish to the bobbing mass that moves with piles of greasy foam on the water's surface. "No, it feels good," smartly replies one young man who looks to be no more than 15 years old. "Besides, I don't have any money."

These desperate job seekers, many from poor rural regions of central and southern Mexico, are risking their lives. The New River, which flows north from Mexicali through California's Imperial Valley to the Salton Sea, contains organisms that cause communicable diseases such

as hepatitis A and cholera, according to health officials. Fecal coliform counts range from 100,000 to five million, well above the count of 400 needed to close swimming beaches. The waterway also picks up pesticide runoff from local farms and hazardous wastes from Mexicali's *maquiladoras*, foreign-owned factories.

The river is so polluted that U.S. Border Patrol agents are forbidden from diving in to catch the illegal immigrants. Several agents have needed medical attention after brief exposure to the river. Many immigrants who are caught eventually end up in local hospitals, where they are treated for skin infections or other external problems, according to Richard Rees, an emergency room physician at the El Centro Regional Medical Center. Those who escape usually do not seek medical attention for fear of deportation.

In addition to exposing themselves, the migrants may be exposing others—in the fields, factories and restaurants where they find work. The Centers for Disease Control and Prevention found that California has twice the rate of infections of two food-borne pathogens associated with human sewage—*campylobacter* and *shigella*—of any other state tested, leading some experts to wonder about a connection. Along the Texas-Mexico border,



MIGRANTS enter California through the befouled New River, which contains microbes responsible for communicable diseases such as hepatitis and cholera.

JEFFREY L. BROWN/Aurora

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health officials are battling tuberculosis brought in by undocumented workers. Of the 17,651 apprehended last year in the Port Isabel, Tex., region, 49 percent tested positive for the TB bacterium. The rate of full-blown tuberculosis in the lower Rio Grande Valley, a fertile agricultural area that borders Mexico, is triple the national average, says Abraham G. Miranda of the U.S. Public Health Service in Port Isabel.

Because law enforcement waits until the immigrants scramble out of the river several miles downstream before giving chase, the odds are pretty good that most will initially escape detection. Indeed, in April border patrol agents were detaining between 25 and 75 illegal immigrants a night at the river, but we counted 80 people floating by in just the first hour.

Federal officials say the problem with migrants in the waterway is getting worse. "They've always used the river, but not to this extent," notes Henry Rolon, spokesman for the U.S. Border Patrol office in nearby El Centro, Calif. "They have no idea how dangerous it is and what kind of illnesses and diseases are in this water." The increase stems from tougher action that has effectively shut down the more traditional border crossings between Tijuana and San Diego: apprehensions in San Diego dropped from 500,000 in 1994 to 182,267 in 1999. The crackdown pushed immigrants to seek more perilous routes.

In light of the pollution problems, the U.S. Environmental Protection Agency is helping fund \$50 million in improvements to Mexicali's sewage treatment plant in conjunction with the North American Development Bank, an agency created by the North American Free Trade Agreement, and a consortium of Japanese *maquiladora* owners. Despite the improvements, the city's wastewater collection system is so antiquated that it needs to be replaced as well, which may take four years.

In the meantime, Mexico has stepped up patrols and posted warnings at river crossings, according to Rita Vargas, Mexico's consul in Calexico. Still, those efforts are overwhelmed by the sheer numbers of people willing to risk their lives. "The main problem we face is smugglers," Vargas says. "They decide the points to cross. Migrants come from the interior. They don't know anything about the border. They think it's easy to cross, but they don't have any information about pollution and the consequences." —Eric Niiler

ERIC NIILER is a freelance science writer based in San Diego.

GEOPHYSICS_HAZARD PREDICTION

Raging Rivers of Rock

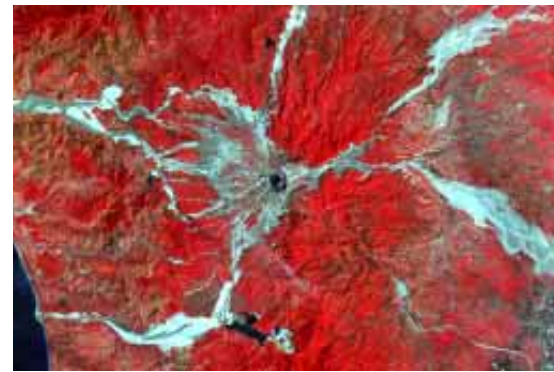
New ways of predicting the disastrous flows of volcanic ash known as lahars

Volcanologist Peter J. Mouginis-Mark nestled a cooking pot filled with cool water into a shallow trench outside his tent. Then he rinsed his hands in a nearby stream that almost scalded his fingers. Half an hour later the water in the pot, too, was hot to the touch.

Had Mouginis-Mark not expected to camp on a colossal bed of volcanic ash, his sizzling surroundings might have sent him fleeing for home. But last November he and four companions from the University of Hawaii hiked up the steep western flank of the Philippines' Mount Pinatubo to explore this very locale. What Mouginis-Mark didn't expect was so much heat, still lingering from Pinatubo's last eruption, in 1991. That blast, the world's largest in 80 years, dumped more than five cubic kilometers of ash on the mountain's slopes. "The high temperature seems to be preventing vegetation from taking hold," Mouginis-Mark says. And with no root networks to stabilize the debris, rain is bound to wash it into the populated lowlands.

And so the volcano sheds its waste—with a vengeance. Time and again, monsoon-soaked slurries of mud and rock surge downhill like wayward loads of

wet concrete, destroying bridges, homes, lives—often causing more devastation at low elevations than the volcanic eruption itself. These violent flows, known by their Javanese name, *lahar*, carry everything from talcumlike particles to boulders the size of sport utility vehicles. Intensified by their steep profiles and heavy loads, lahars travel much faster than clear-water streams—in some in-



AFTER THE BLAST: Vegetation (above, red) reinhabited much of the volcano's ash-covered slopes within five years of the 1991 Mount Pinatubo eruption, but hot, barren ash deposits (gray) remain vulnerable to lahars, which can carve valleys dozens of meters deep (below).



PETER J. MOUGINIS-MARK University of Hawaii

stances, up to 100 kilometers per hour.

Such is the recurring threat at hundreds of volcanoes worldwide. But exploring potential lahar hazards by foot takes a lot of time, and in remote or war-torn regions such fieldwork is impossible. That is why Mougini-Mark and other researchers have turned to satellite imagery and specialized computer programs to help them more efficiently predict where and when lahars may strike.

During a mission completed in February, a space shuttle crew used cloud-piercing radar to measure the heights of about 136 billion points on the earth. Scientists are now translating those numbers into digital maps that show the topography of the land surface in pixels 30 meters square and 16 meters high. Mougini-Mark and his colleagues plan to compare that close-up view of Pinatubo with height and width measurements of lahar-swept valleys they took in November. Combined with other satellite records of surface temperature and vegetation, precise topography can help them predict which depressions future lahars may follow and where the next center of activity will be. And none too soon: judging by the amount of rubble still covering Pinatubo's slopes, lahars may continue for another 10 or 20 years, says Ronnie Torres of the Philippine Institute of Volcanology and Seismology in Quezon City.

Halfway around the globe, scientists are pursuing a different approach to lahar prediction. Richard M. Iverson of the U.S. Geological Survey's Cascades Volcano Observatory in Vancouver, Wash., and two colleagues painstakingly computerized the paths of dozens of past lahars. Now, with an estimate of the volume of ash and debris blanketing a hillside, plus the downslope topography, the computer can generate detailed maps of the areas that lahars are most likely to ravage. Again, precise topography is the key to trustworthy predictions: "If you miss a ridge five or 10 meters high that separates a valley from a city, you can really make a bad mistake," says Iverson, whose team also mixes its own water-and-ash recipes and watches them rage down a 95-meter-long concrete chute to study how lahars transport debris.

Almost as soon as Iverson's team perfected its computer program—it accurately re-creates well-understood ancient lahars on Mount Rainier—it was recruited to make a prediction. Quito, Ecuador, a city of 1.8 million people, lies a mere 10 kilometers from the summit of Guagua

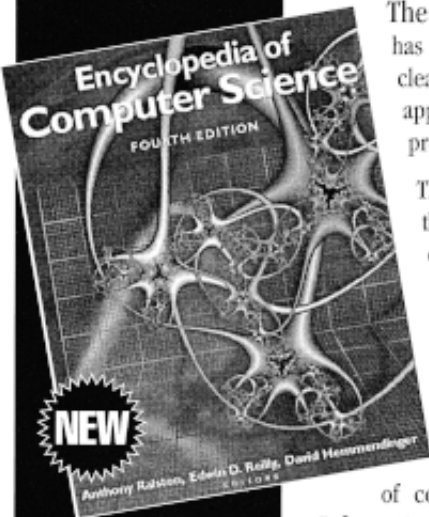
Pichincha, which began to wake up in August 1998 after more than three sleep centuries. City officials quickly called on the USGS Volcano Disaster Assistance Program, the same crisis response team that helped to predict Pinatubo's 1991 eruption. For the first time, the team added the lahar prediction program to its volcano-monitoring strategy. The computer program forecasts that lahars will likely inundate Quito's western edge if a big eruption occurs. The hazard maps have since appeared on the front page of city news-

papers to alert people about which neighborhoods to evacuate in an emergency.

Back in the Philippines, Torres and others are revising lahar hazard maps for Mayon, the country's most active volcano. They must account for about 30 million cubic meters of ash and lava deposited during a February eruption. Monsoon season has begun, but despite the imminent danger Torres remains optimistic. Unlike earthquakes and other geologic hazards, "lahars are a visible adversary," he says.

—Sarah Simpson

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ENTOMOLOGY

Beetle to Bee

Tiny blister beetle larvae in the Mojave Desert are taking bees for a ride. Hundreds of the parasitic *Meloe franciscanus* beetles clump together to mimic the shape and color of a female bee. When an amorous male bee attempts to mate, the beetles grab his chest hair and are carried off. When the duped male mates with a real female bee, the beetles transfer to her back and ride off to the nest, where they help themselves to pollen. The cooperative behavior of the beetle larvae, described by John Hafernik and Leslie Saul-Gershenz of San Francisco State University in the May 4 *Nature*, is virtually unknown in the insect world except among social species such as bees and ants. The report also notes that beetle clumps must also smell like female bees, because the male bee is not fooled by painted models. *Diane Martindale*



Come hither, yon bee

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MOLECULAR BIOLOGY

Age of the Clones

When Dolly the cloned sheep was born, scientists wondered whether she would live a normal life span—more than a decade—or whether she would live out only the remaining years of the six-year-old ewe from which she was cloned. At first, Dolly's fate looked bleak: age-related structures at the tips of her chromosomes, called telomeres, appeared shorter than they should be for a young sheep. But researchers now suspect that Dolly's shortened telomeres were a fluke. In April a group led by Robert P. Lanza of Advanced Cell Technology in Worcester, Mass., reported in *Science* that cloned cattle have *longer* than normal telomeres and that their cells divide in cultures many more times than usual. The results bode well for using cloned human cells as a source of replacement tissues and organs that won't expire prematurely. *—Carol Ezzell*



COURTESY OF ADVANCED CELL TECHNOLOGY

SENSORS

Nanobending

The melding of silicon with biology has taken a step forward, thanks to recent advances by the IBM research center in Zurich and the University of Basel. In the April 14 *Science*, the researchers report that they constructed a biomolecule sensor based on an array of minuscule silicon piers—each thinner than $\frac{1}{50}$ of a human hair. Each fingerlike cantilever is coated with a different short DNA molecule that will bind only with

complementary DNA strands added later. The extra DNA stresses the fingers, causing them to bend by about 10 nanometers. A laser beam detects this curving. Possible applications of the sensor, which can register a single DNA-base mismatch, include rapid diagnostic assays and implanted nanorobots that deliver drugs by using the body's own molecules to operate tiny mechanical valves. *—Julia Karow*



Silicon fingers

IBM RESEARCH AND UNIVERSITY OF BASEL



OVERLOOKED IN THE ANNALS OF GEOLOGY:
THE FIELD WORKERS WHO FIRST CAME ACROSS THE
CHANGING ROCKS OF KARAKUZA—RAW MATERIAL
FOR THE MOOD RING

SIDNEY HARRIS

NOMENCLATURE

Einstein's Constant

What's in a name? Perhaps more than Shakespeare would have us believe. In April, Kenneth Brecher of Boston University proposed that the venerable old "speed of light" (in a vacuum) be renamed "Einstein's constant," thus echoing Newton's constant of gravitation and Planck's constant of quantum mechanics.

Einstein's constant is more fundamental than just a property of light: it defines the relation between space and time and between matter and energy (the famous $E = mc^2$) and is intimately related to questions of cause and effect. The new name could also make it less confusing to discuss the optics of media such as water, where light travels slower than Einstein's constant.

—Graham P. Collins



SHARON STEUER

DATA POINTS

Do You Want Fries with That?

Number of illness outbreaks in the U.S. in 1997 caused by:

Food in the home: 113
Food in restaurants: 216

Percent of foodborne illnesses caused by:

Pork:	0.4	Fruits and vegetables:	6.0
Milk, Eggs:	1.0	Salads:	12.4
Fish, Shellfish:	1.3	Unknown:	41.3
Chicken:	2.1		
Beef:	2.5		

Daily per capita food calories consumed in the U.S. in 1909: 3,500

Total fat consumed: 123 grams

Daily calories consumed in 1994: 3,800

Total fat: 159 grams

Number of undernourished people in the world: 1.2 billion

Number of overweight people: 1.2 billion

SOURCES: Morbidity and Mortality Weekly Report; U.S. Department of Agriculture; Worldwatch Institute



DEBORAH VAN KIRK/The Image Bank

ROBOTICS

Droids versus Fires

HARTFORD, CONN.—The robot inched toward the candle, bringing the balloon closer and closer to the flame. Finally, it popped, the candle went out, and the crowd went wild. Elsewhere in the Trinity College gymnasium, fourth-graders and veteran engineers milled around, excitedly swapping computer code, cheering on their competitors and hastily reworking their mechanical creations. For amateur robot builders, the seventh annual Fire-Fighting Home Robot Contest this past April was the world's largest and perhaps hardest competition.

In the better-known Robot Wars, held in San Francisco, the cyborgs are remote-controlled, but at Trinity they are on their own. Each must navigate a model house 98 inches square, locate a candle placed at random and extinguish it. Some were made from Lego Mindstorms kits, others from custom-machined parts. Often the cheapest robots were the cleverest, poverty being the mother of invention. One had four wheels,

each of which pivoted to change direction (which would be handy for parallel parking). Another waddled along on two paddle feet, using its heavy head as a counterweight to take each step. Besides the bursting balloon, fire-beating bots relied on fans, water guns and CO₂ cartridges to douse the flame. Some never made it that far, spinning helplessly in a tight circle or confusedly battering the candle rather than blowing it out from a safe distance.

In 1994 only one of the 10 entrants found the flame, and it took over three minutes. This year, of 132 robots from 23 states and eight other countries, 81 did so—some in under 10 seconds. First place in the junior division went to students from Herzliyya Hebrew Gymnasium, a high school in Tel Aviv; in the senior division, to students at Zur Institute for Industrial Education, a technical college in northern Israel. Says organizer Jake Mendelssohn, an adjunct engineering professor at Trinity, "I really believe that in a few years, there'll be real devices like this in our houses."

—George Musser

MRS. STAMPY, a waddling robot built by Mark Whitney, a software engineer from Cary, N.C., won the prize for Most Unique Robot Design at the Trinity College robot contest.



MARK WHITNEY

The Search for Extreme Life

If microorganisms exist on other worlds, the head of NASA's fledgling Astrobiology Institute plans to find them

The relentless heat cooks the Badwater region of California's Death Valley so thoroughly that some expanses are textured like dry serpent skin. At some 284 feet below sea level—North America's lowest point—it is perhaps the hottest place on the surface of the earth: the temperature once peaked at a record 53.01 degrees Celsius (127.4 degrees Fahrenheit). Out here, blood-pumping mammals are scarce. It may seem unfitting to find a Nobel Prize winner, renowned for hepatitis B work, in this scorching pit. But Baruch S. Blumberg's latest challenge takes him beyond human subjects. As the first director of the National Aeronautics and Space Administration's Astrobiology Institute (NAI), he is searching for extreme life-forms, the kind

the space agency aims to someday find on other worlds.

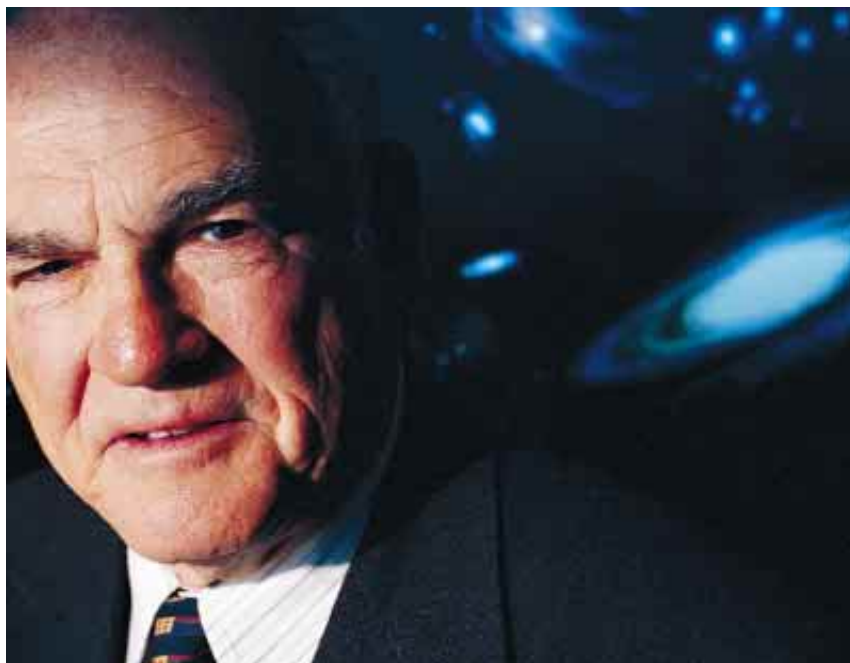
"I always liked the idea of doing field-work, exploring, going out and finding new things," Blumberg says back at NAI headquarters, which is nestled near Silicon Valley at the NASA Ames Research Center at Moffett Field. Out of his desert garb, the outdoors-loving Blumberg looks a good decade younger than his 75 years. At the job only since last September, Blumberg is trying to marshal gaggles of astronomers, chemists, ecologists, geologists, biologists, physicists and even zoologists. He is convinced that advances in molecular biology, space exploration and other endeavors make timely the reexamination of such age-old issues as the origins of life and its possible existence elsewhere.

"Technology is available to decipher the intricacies of this cause-and-effect chain" that wasn't available even five years ago, Blumberg notes, citing in particular advances achieved through the Human Genome Project. The 1996 announcement of potential fossilized life in a Martian meteorite known as ALH84001 boosted enthusiasm worldwide. Even Congress, which had quashed NASA's search for extraterrestrial intelligence (SETI) program in 1993, became receptive. On sabbatical at Stanford University in 1998, Blumberg, along with scores of others, helped to craft NASA's Astrobiology Roadmap during a series of workshops. It defined the role for the new institute.

"With NASA's Astrobiology Institute we are witnessing not just a shift in scientific paradigm but, more important, a shift in cultural acceptability among scientists," says extrasolar planet hunter Geoffrey W. Marcy of San Francisco State University. Already Blumberg's institute is becoming "the intellectual basis for a broad range of NASA missions," says NASA administrator Daniel S. Goldin. Goldin hopes to raise the NAI's budget from about \$15 million to \$100 million within five years. The NAI now comprises some 430 astrobiologists at 11 universities and research institutions.

Although the institute is lending new credibility to the search for extraterrestrial life, *X-Files* fans needn't hold their breath. Unlike the now privately funded SETI program, which focuses on radio transmissions and other hallmarks of presumably sentient beings [see "Where Are They?" by Ian Crawford, on page 38], the NAI is targeting microorganisms and other, even more primitive evidence of lifelike matter. Specifically, the NAI is looking for life in hostile environments—in deserts, volcanoes and ice caps; down thousands of meters below Earth's surface or into the ocean; and on Mars, Jupiter's moon Europa, Saturn's satellite Titan, even planets beyond the solar system.

For now at least, extremophiles on Earth offer the most probable model for testing the hypothesis that life exists elsewhere. NAI researchers hope to use genomic



BARUCH S. BLUMBERG: NONEXTREMOPHILE

- Born July 28, 1925: "A very optimistic time"
- Wife, Jean, a painter; daughters, Anne and Jane; sons, George and Noah
- Most Important Field Trip: The Philippines in 1967 to test hepatitis virus theory
- Best-Known Fact: Won 1976 Nobel Prize for Physiology or Medicine
- Least-Known Fact: His rustic western Maryland farm lacks indoor plumbing
- On Extraterrestrials in Our Solar System: "Highly evolved life is very unlikely, but we have to continue our search"

databases of key microorganisms to link evolutionary sequences with geochemical and paleontological events. Another desire is to launch DNA microprobes on board miniature spacecraft to search for signs of life. Answers, if they ever come, may take many decades.

Blumberg believes his past biochemical work gives him intimate insights into life-forms, whether of this world or not. "One of the things about doing medicine and medical research is that you really get a kind of feeling for the organism that you work with," he observes. Hence, profound questions of life "are coming directly and indirectly into your thinking."

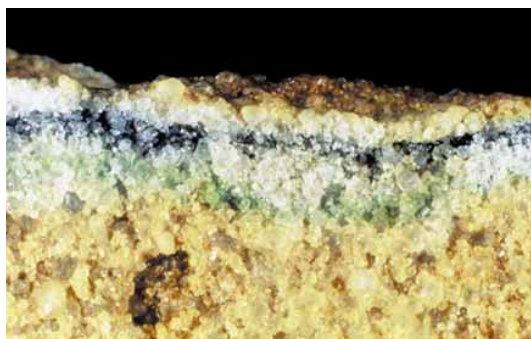
As a child in a tight-knit immigrant community in Brooklyn, N.Y., Blumberg checked out book after library book on the reigning explorers. "Amundsen, Peary, Scott, Shackleton, Rae, Nansen were common names in my circle of friends," he recalls. "I believe this had an effect on my seeing science as discovery. My interest in fieldwork also fed into this." To this day he collects books on early travel and Arctic expeditions.

After graduating from Far Rockaway High School in 1943, he enlisted in the Naval Reserves and secured a physics degree at Union College in Schenectady, N.Y. At age 21 he made captain of a small U.S. Navy ship. "It is a great sensation to plot a course, take a few sights, do some dead reckoning, and end up more or less where you had predicted. It gives one confidence in the power of applied mathematics and the effectiveness of rational solutions." Captaining that crew 24 hours a day instilled an unshakable confidence in him. "I assumed that I would have leadership roles in whatever I did," he says.

In 1946, thanks to the G.I. Bill, Blumberg started graduate school in mathematics at Columbia University, only to transfer a year later to the medical school at the behest of his attorney father. For his medical internship and residency, Blumberg picked the crowded, understaffed wards of New York City's Bellevue Hospital, where the poor and chronically ill were typically sent. "And this was before health insurance," he emphasizes. Bellevue taught Blumberg a new definition of responsibility: "The fact that you've got to do it—if you don't do it, nobody else will."

Equipped with an M.D., he decided to

pursue his own longing to be a scientist and went in 1955 to the University of Oxford, where he began his doctorate in biochemistry under Alexander G. Ogston. At the time, Oxbridge was buzzing with excitement over Watson and Crick's discovery of the DNA double helix. Blumberg himself had become intrigued with inherited genetic variations a few years earlier. In 1950 he had gone to a desolate mining-town hospital in Suriname in South America, where, besides witnessing the devastation caused by infectious diseases, he observed large differences in susceptibility to the elephantiasis parasite among diverse immigrant workers. A 1957 field trip to West Africa formally launched his study of such genetic variations, called polymorphisms, which he would continue at the National Institutes of Health.



CRYPTOENDOLITHS—microcolonies of fungi, algae and cyanobacteria (colored layers)—thrive inside this sandstone rock from cold and dry Antarctica, showing that life can exist in hostile conditions.

Blumberg collected data on the distribution of polymorphisms. Initially, he culled blood for clues to disease resistance. To find possible variants, he and his colleagues relied on the natural immune response to compare blood proteins from frequently transfused patients, mainly hemophiliacs. From antibodies in the patients' bloodstream, they could derive foreign antigens. In 1963 Blumberg's team isolated a peculiar variant and dubbed it "Australian antigen." Common among Australian Aborigines, Micronesians, Vietnamese and Taiwanese, the blood protein was rare among Westerners. The team, however, observed it in leukemia patients in the U.S., who also were receiving transfusions. The researchers set off exploring whether the unusual antigen played a role in susceptibility to leukemia.

Instead of an inherited immune factor, the curious surface antigen proved to be part of the then mysterious hepatitis B virus. "His discovery of Australian antigen

was the Rosetta stone for unraveling the nature of the hepatitis viruses," comments Robert H. Purcell, head of the NIH's hepatitis lab.

This key finding enabled researchers to develop the first blood test to screen for the virus, thus protecting blood supplies. In 1969 Blumberg and microbiologist Irving Millman patented a strategy to develop a hepatitis B vaccine. Their novel approach relied on purifying from the virus those very same surface antigen particles—which by good fortune proved not only to produce protective antibodies but to be noninfectious. For advancing understanding of the mechanisms of infectious diseases, Blumberg shared the 1976 Nobel Prize for Physiology or Medicine.

A commercial vaccine based on Blumberg's method, now made using recombinant DNA techniques, has saved tens of millions of lives, according to World Health Organization estimates. Blumberg remains optimistic that hepatitis B can someday be eradicated, but today the virus continues to kill more than a million people a year, including 5,000 in the U.S.

When not working, the Nobel laureate prefers to birdwatch or kayak or even shovel manure on a cattle farm he owns with friends in western Maryland. "That kind of manual labor is an antidote to too much thinking," he says.

In Death Valley, Blumberg and other researchers, led by Christopher McKay of NASA Ames, used syringes to extract heat-loving microbes for DNA analysis back at the lab. Blumberg plans to accompany researchers on other field trips to collect extremophiles, perhaps in Mongolia's Gobi Desert or in Antarctica. Tests of new robots for planetary exploration might even send him to the Canadian Arctic.

Besides guiding and inspiring his researchers, Blumberg wants to take advantage of powerful computers to model how life might evolve elsewhere. "Astrobiology lends itself to iterated induction-deduction exercises, as well as theory and model construction," Blumberg explains. He notes wryly that in this field "there's a high probability you will reject the model." Just the same, he and his followers hope the conditions that allow life to flourish on Earth exist elsewhere in the Milky Way and beyond. "It could happen," Blumberg says. "In any case, you have to go and look." —Julie Wakefield

JULIE WAKEFIELD writes frequently on science and technology. She is based in Washington, D.C.

MEDICINE_TISSUE REPAIR

Scar No More

Biodegradable scaffolds give skin cells a better road map for self-repair

In the quest to heal wounds without leaving a scar, researchers have looked at some 3,000 treatments. Many have not lived up to expectations, and none can induce repair that leaves the skin in pristine condition. Now U.S. and British scientists have come up with three different recipes for advanced bandages that jump-start the repair of injured skin but then break down, leaving behind only healed tissue. Such biodegradable scaffolds eliminate the need to change dressings, cut the risk of infection and improve the odds of scarless healing.

When skin is injured, the weave-like structure of collagen fibers, the skin's glue, is destroyed. To minimize blood loss and infection, the body opts for a quick fix: it marshals cells called fibroblasts, which lay down thin, linear strips of replacement collagen. When skin cells grow on the replacement collagen, they produce pale, less flexible ma-

terial. Avoiding this scar tissue means getting the body to rebuild the complex fibrous structure of the original.

An aggressive, active therapy relies on tissue cultured in the lab for use as a temporary patch. Organogenesis in Canton,



PORK BANDAGE: Pig intestines, converted here into a sheet, can induce wound repair with minimal scarring. They also come in powder and gel forms.

Mass. (makers of Apligraf), and Advanced Tissue Sciences in La Jolla, Calif. (developers of Dermagraft), both depend on foreskin from circumcised newborns. The foreskin cells are grown on substrates, resulting in layered matrices that secrete growth factors. Although Dermagraft is waiting for the same regulatory approval given Apligraf in 1998, both have already aided thousands of patients. But the costly engineered tissue would be inappropriate for smaller sores that may heal naturally with just the right kind of dressing.

Ronald A. Coffee, a University of Oxford biochemist and president of the Oxford-based biotech company Electrosols, has a spray-on dressing he hopes will encourage normal skin growth immediately after an injury. The spray consists of a synthetic polymer (the same as that used for dissolving stitches) mixed with ethanol and placed in a small, high-tech dispenser that could be mistaken for a prop on the set of *Star Trek*. An applied electrical field charges the mixture, a step "that turns out to be the key to the whole thing," Coffee notes. Because the wound is at a far lower electrical potential than the polymer is, the solution is attracted to the skin and flies out through a tiny nozzle, producing fine, light fibers, each of them two microns in diameter.

From Vitamin E to Z-Plasty

Plastic surgeons have more than one trick to remove a scar

Scarless healing with bioscaffolds may be on the horizon, but meanwhile millions more scars will form. Patients seeking to get rid of scars have several options, depending on the depth of the scar, says Elliott H. Rose, director of the Aesthetic Surgery Center in New York City. Superficial ones can be reduced, smoothed down and blended into the surrounding skin by steroid creams or injections and by a surgical sanding technique known as dermabrasion. Lasers can greatly diminish some scars by instantly vaporizing the outer layers of skin. Silicone gel sheets, mineral oils and vitamin E may improve new scars. For Liana Gedz, whose unstable physician, apparently proud of his work, carved his initials, "AZ," into her belly after giving her a cesarean section (*photograph*), Rose says he would do a mini-tummy tuck—that way, even the C-section scar would be hidden.

For a more severe and deeper scar, surgeons will perform Z-plasty, a technique that repositions the scar to the natural crease lines of the skin. If a large area of skin has been lost, as

with burn victims, a surgeon will remove the entire scar and shift a piece of healthy skin, along with the underlying fat,

blood vessels and muscles, to the injured site. In cases where a flap is not possible, a regular skin graft is used.

To reduce the "ice pick" appearance of acne scars, Rose liposuctions fat from the patient to fill in the depressed pits. Any excess is frozen for later use, in case the fat filling gets reabsorbed into the body. But for raised keloid scars, he prefers radiotherapy following scar removal, killing the cells responsible for excessive growth with high doses of radiation.

Despite all this technology, however, one fact remains: once scarred, always scarred. "You can't airbrush out a scar," Rose explains, "but you can create great camouflage." —D.M.



INITIALED, but not for life.

The fibers have the same charge, so they repel one another and regularly space themselves like a textile weave. The collagen-forming fibroblasts, however, are attracted to the charged fibers. The woven pattern of the fibers makes the difference; the cells use it as a road map to re-create the original collagen structure. Coffee believes that controlling the formation of collagen in this way will lead to normal skin growth instead of scarring.

The inventors predict that spray-on fibers could treat everything from minor cuts to third-degree burns, and because the device is so small it could easily be carried by paramedics and kept in first-aid kits. Coffee is confident the fibers will work, although he admits that thus far only one human patient, a colleague at the company, has successfully used the spray. The technique has potential, but animal and human trials are needed to determine how the spray works in the body, points out Mark W. J. Ferguson, an expert in wound healing at the University of Manchester. "A person's immune system can demolish and reabsorb the scaffold before the cells have a chance to migrate on it," he says. The scaffolds could also cause inflammation, which would interfere with scarless healing.

If the spray-on method flops in clinical trials, a less futuristic treatment might work: a three-layer dressing incorporating chitosan—a fiber derived from crab shells, 350 million pounds of which are discarded in the U.S. annually. Applied to the skin, the scaffold provides a base for cell growth. It encourages cells to grow back only from the edges of the chitosan layer, thus preventing renegade cells from erupting below the wound, which would contribute to scar formation.

The dressing, which is being developed at North Carolina State University, also incorporates two other layers: a starch-derived polymer, which transports away pus and protects the wound as the chitosan breaks down, and an outer cotton gauze, which can be changed as needed without bother to the wound. The body eventually absorbs both the chitosan and polymer layers, leaving behind intact skin. "It's ideal for burn injuries, since the dressing never has to be disturbed," remarks North Carolina State's Bhupender S. Gupta, who is developing the dressing with colleagues Samuel M. Hudson and Alan E. Tonelli.

To make the dressing, the researchers grind crab shells to a fine powder and mix it with chemicals to convert the base material, chitin, into chitosan. They then

pour the resulting viscous liquid onto Teflon sheets to create a thin film. In addition to its healing abilities, chitosan has natural infection-fighting properties: fungi, viruses and other microbes seem unable to live on it. The team also hopes to streamline manufacturing and to design a second-layer polymer that will allow delivery of medications to the injured skin.

So far results are positive, based on studies in pigs. But, as with the spray-on fibers, clinical trials are needed to see how well the dressing performs on human skin, and Gupta says it will be several more

years before consumers see it on pharmacy shelves.

There is a high-tech scaffold that's commercially available now, and it comes from a source as unexpected as crab shells: the small intestines of pigs. Ten years ago Purdue University scientists isolated the layer of tissue called small intestinal submucosa, or SIS, and found that it had unusual healing properties. It contains a complex matrix of collagen, growth factors and other proteins that, when applied to a wound, functions as a natural framework that prompts the body to

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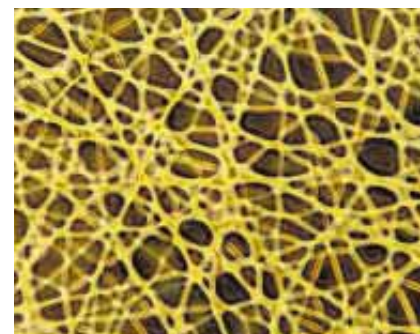
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POLYMER MAT from a spray-on dressing provides a framework for skin regrowth.

build new tissue with little or no scarring. "It's been referred to as a playground for cell growth," says Neal Fearnot, president of Cook Biotech in West Lafayette, Ind., which has begun marketing the dressing under the name OaSIS. It has already been used in humans to cure chronic sores and to treat severe skin injuries that might otherwise result in amputation.

OaSIS is easy to make and doesn't cost much; the small intestine is a throwaway product from pork production, and a single pig can donate up to 90 feet of it. The isolated SIS material is first washed and sterilized; then unwanted surrounding cells are stripped away before it is freeze-dried. The result resembles parchment paper. Applied to a wound, it stimulates new blood vessels to form, creating a pipeline that can nourish the newly implanted scaffold (chronic sores are often caused by poor circulation). As the new tissue grows, the body dismantles the intestine-derived material and replaces it with the same tissue type there originally.

The transfer of pig viruses to humans is unlikely. "Porcine products have a good history with humans; pig skin has been used for years to treat burns," points out Purdue biomedical engineer Stephen F. Badylak. Some patients, though, may be allergic to pig products.

Considering that some five million wounds, many chronic, will occur this year in the U.S., "these advanced wound-healing technologies are like penicillin" in an epidemic, says Harold Brem, director of the Wound Healing Center at Mount Sinai Hospital in New York City. Brem, who treats up to 100 patients a week, cautions that many fancy dressings parade as agents that speed up skin repair, but most can't even start the healing process. Biodegradable scaffolds might not win the healing race, but if they live up to their promise, at least there won't be a scar in sight. —Diane Martindale

Unplugged but Unbowed

In the more than five years since Kevin Mitnick was arrested and sent to prison, the Internet has grown by a factor of 16 and CPU speed has increased by a factor of eight. Even new computer languages and operating systems have risen to prominence and become cheaper; the OS source code that Mitnick stole from Sun Microsystems, a copy allegedly worth \$80 million at the time, now retails for \$100. But breaking into computers has not grown significantly more difficult, the recently paroled hacker told questioners at a May e-business conference in New York City sponsored by *Business Week*.

Mitnick, who began breaking into telephone systems and computers in the late 1970s, was captured by the FBI in 1995 after a two-year chase that yielded front-page headlines and a six-figure advance for the journalists who made him an icon of modern techno-legend. But for now, he may be a different kind of legend: the only completely unplugged nerd in the country.

After more than four years of pretrial detention, he pled guilty last year to one count of computer hacking and four counts of wire fraud for making telephone calls in which he lied to get restricted information. Federal prosecutors dropped 20 other charges in return for the plea. Mitnick was released from federal prison in January, on condition that he neither possess nor use any computer or telecommunications equipment other than a hardwired telephone for the next three years.

Mitnick's lawyers contend that strict interpretation of these rules bars even work at McDonald's, where computers operate cash registers and cooking equipment. Meanwhile, as part of a ban on employment in computer-related fields,

Mitnick's probation officer has forbidden him to accept speaking engagements, but he is allowed to testify before Congress and to answer questions from the media at public events without risking a return to prison. (When he participates in an on-line chat, an intermediary reads questions to him from the screen and transcribes his answers.)

Speaking over a video link, Mitnick told his interlocutors that he had kept himself up-to-date by reading magazines and computer textbooks and concluded that the same security holes still exist: the heart of most of his exploits was social rather than technical.



PAROLED HACKER Kevin Mitnick, shortly after his release in January.

Computer wizardry alone served him for less than a third of his break-ins, he estimated, and "social engineering" accounted for the rest. During his time on the wrong side of the law, he recalled, he was often able to gain access to computers at large companies by playing one division against another or by using jargon that only an employee would usually know. The "I LOVE YOU" e-mail virus epidemic of late April and early May shows that most computer

users are still vulnerable to even the simplest ruses, he observed. (He also criticized the development of integrated software and operating systems that make such malicious programs easy to develop and propagate.)

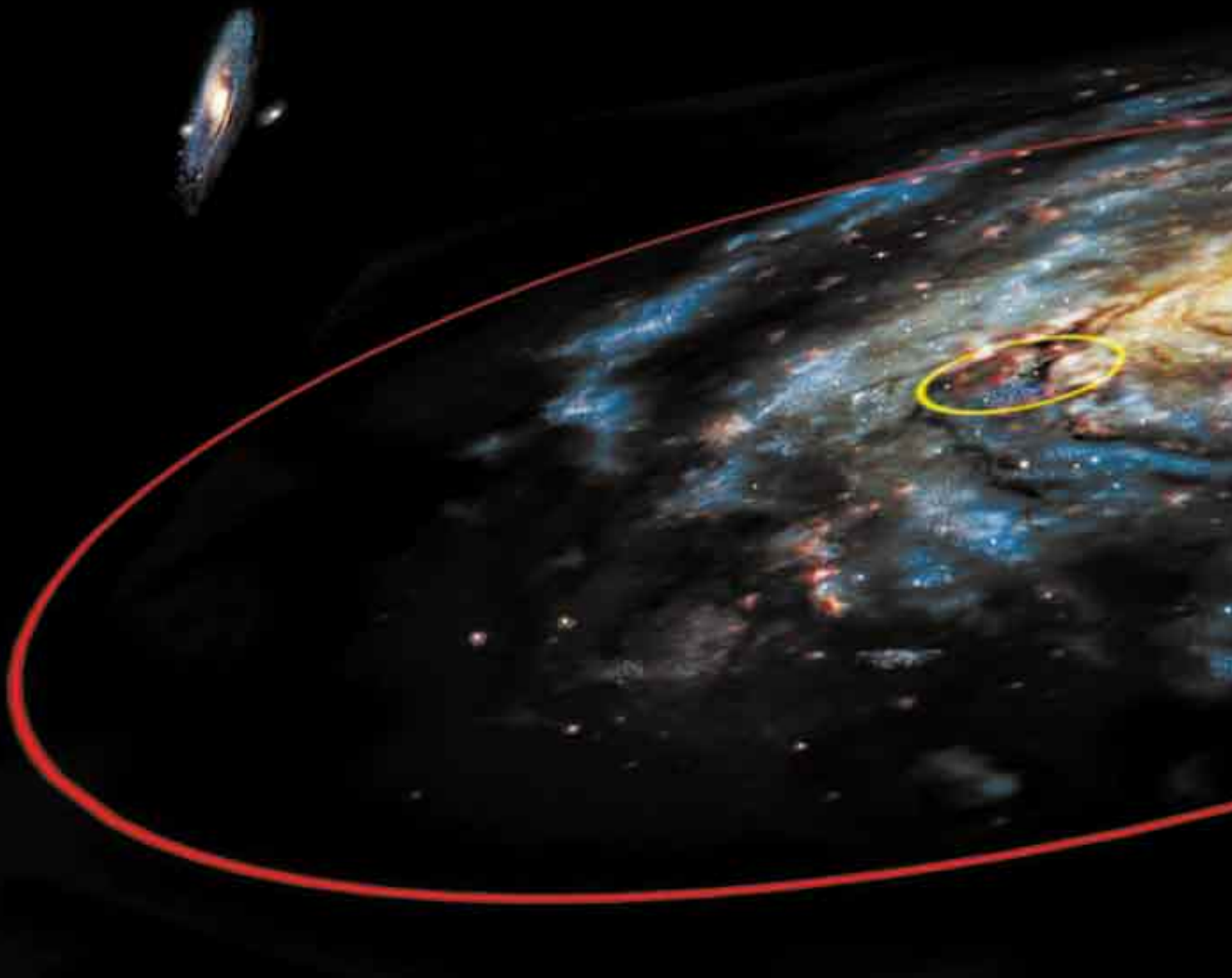
"Training is as important as crypto," Mitnick maintained. Although codes to safeguard information have their place, "you need education for each new hire so that they're not scammed." And the same kind of subterfuge that causes employees to open a virus-laden attachment could also lead them to unknowingly install programs that ship all their data to unscrupulous competitors.

For all the attention that Internet businesses give to preventing digital break-ins and safeguarding information as it is transmitted, they sometimes neglect other, much simpler dangers. Consider the example, Mitnick said, of the company that sends backup tapes—unencrypted—to a low-security warehouse for off-site storage in case of disaster. "You have to look at the big picture," he noted.

Indeed, looking at that picture suggests that even uberhackers of Mitnick's ostensible caliber are fairly far down on the list of e-threats. "The most common threat is a disgruntled employee or ex-employee," Michael Vatis of the FBI told the same audience. He also warned of intrusions by organized crime and even by corporate and government intelligence services. Vatis chided companies for ignoring readily available warnings of security threats, pointing out, for example, that the fix for the denial-of-service attacks that blocked the Internet's biggest Web sites in February had been known since last December. "Government's job is not to be out there manning the barricades," he said. (Similarly, one of the key hacking techniques Mitnick was accused of using in 1994 had been recognized—along with a countermeasure—for more than 10 years.)

Where does this game of attacks and countermeasures leave Mitnick himself? Have more or less professional criminals taken the place of the glamorized knowledge-driven explorer? Vatis comments that the very notion of computer crime is becoming vague as everyday life goes online. Many system administrators report that most of the attacks they see are from "script kiddies"—amateurs trying to break into machines with prepackaged hacking tools that require only a few keystrokes to launch. Mitnick asserted (as he has after previous, lesser convictions) that he intends to go straight and—just as soon as he is allowed—to put his considerable expertise at the service of organizations that need protection from people like him. But in the meantime, in his status as the archetypal digital unperson, he may serve as an object lesson in just how thoroughly wired our society has become.

—Paul Wallich



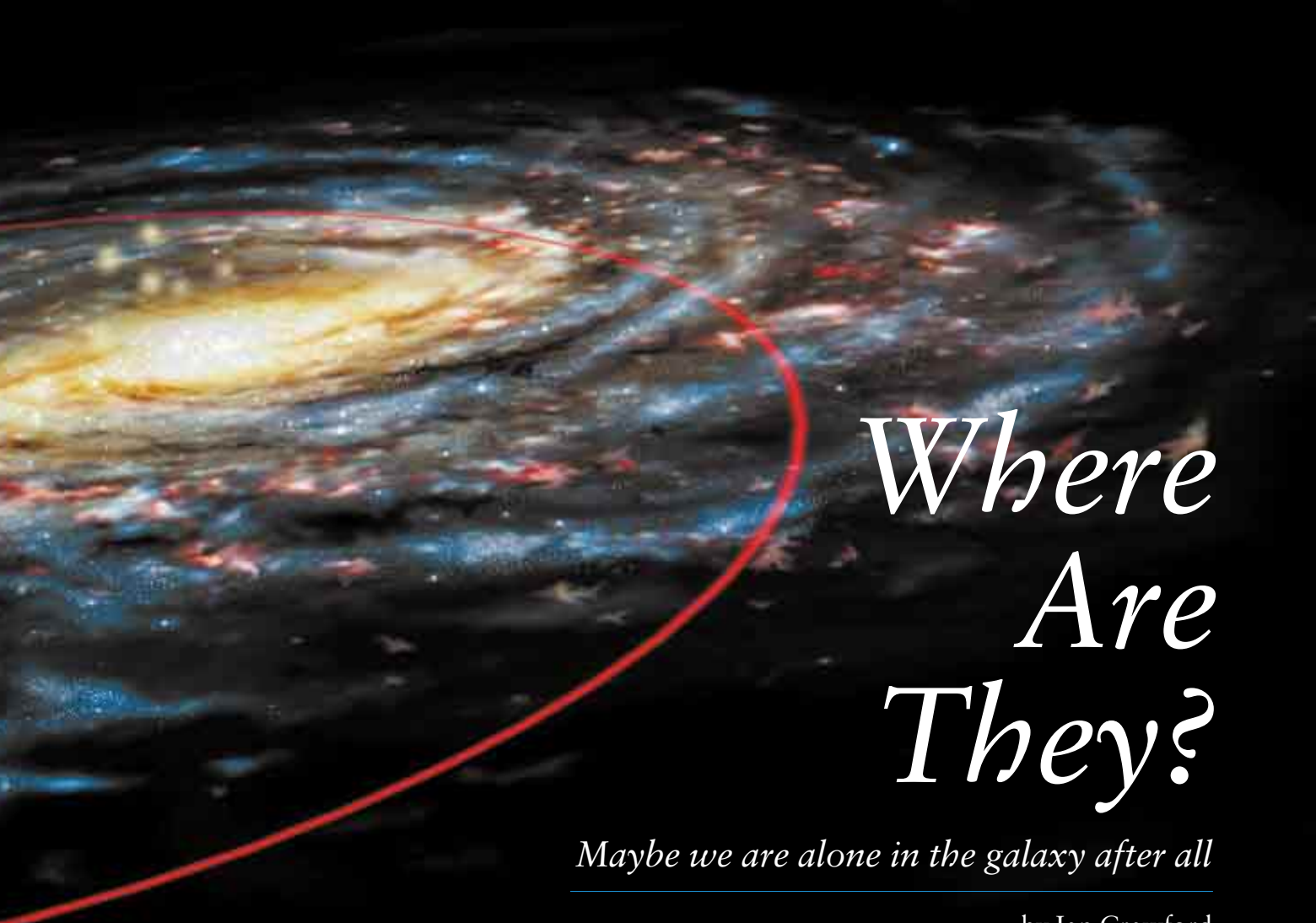
How common are other civilizations in the universe? This question has fascinated humanity for centuries, and although we still have no definitive answer, a number of recent developments have brought it once again to the fore. Chief among these is the confirmation, after a long wait and several false starts, that planets exist outside our solar system.

Over the past five years more than three dozen stars like the sun have been found to have Jupiter-mass planets. And even though astronomers have found no Earth-like planets so far, we can now be fairly confident that they also will be plentiful. To the extent that planets are necessary for the origin and evolution of life, these exciting discoveries certainly augur well for the widely held view that life pervades the universe. This view is supported by advances in our understanding of the history of life on Earth, which have highlighted the speed with which life became established on this planet. The oldest direct evidence we have for life on Earth consists of fossilized bacteria in 3.5-billion-year-old rocks from Western Australia, announced in 1993 by J. William Schopf of the University of California at

Los Angeles. These organisms were already quite advanced and must themselves have had a long evolutionary history. Thus, the actual origin of life, assuming it to be indigenous to Earth, must have occurred closer to four billion years ago.

Earth itself is only 4.6 billion years old, and the fact that life appeared so quickly in geologic time—probably as soon as conditions had stabilized sufficiently to make it possible—suggests that this step was relatively easy for nature to achieve. Nobel prize-winning biochemist Christian de Duve has gone so far as to conclude, “Life is almost bound to arise . . . wherever physical conditions are similar to those that prevailed on our planet some four billion years ago.” So there is every reason to believe that the galaxy is teeming with living things.

Does it follow that technological civilizations are abundant as well? Many people have argued that once primitive life has evolved, natural selection will inevitably cause it to advance toward intelligence and technology. But is this necessarily so? That there might be something wrong with this argument was famously articulated by nuclear physicist Enrico Fermi in 1950. If extraterrestrials are commonplace, he asked, where



Where Are They?

Maybe we are alone in the galaxy after all

by Ian Crawford

are they? Should their presence not be obvious? This question has become known as the Fermi Paradox.

This problem really has two aspects: the failure of search for extraterrestrial intelligence (SETI) programs to detect radio transmissions from other civilizations, and the lack of evidence that extraterrestrials have ever visited Earth. The possibility of searching for ETs by radio astronomy was first seriously discussed by physicists Giuseppe Cocconi and Philip Morrison in a famous paper published in the journal *Nature* in 1959. This was followed the next year by the first actual search, Project Ozma, in which Frank D. Drake and his colleagues at the National Radio Astronomy Observatory in Green Bank, W.Va., listened for signals from two nearby stars. Since then, many other SETI experiments have been performed, and a number of sophisticated searches, both all-sky surveys and targeted searches of hundreds of individual stars, are currently in progress [see “The Search for Extraterrestrial Intelligence,” by Carl Sagan and Frank Drake; *SCIENTIFIC AMERICAN*, May 1975; “Is There Intelligent Life Out There?” by Guillermo A. Lemarchand; *SCIENTIFIC AMERICAN PRE-*

ZIP, ZILCH, NADA has come out of any aliens with whom we share the galaxy. Searches for extraterrestrial intelligence have at least partially scanned for Earth-level radio transmitters out to 4,000 light-years away from our planet (yellow circle) and for so-called type I advanced civilizations out to 40,000 light-years (red circle). The lack of signals is starting to worry many scientists.

SENTS: Exploring Intelligence, Winter 1998]. In spite of all this activity, however, researchers have made no positive detections of extraterrestrial signals.

Of course, we are still in the early days of SETI, and the lack of success to date cannot be used to infer that ET civilizations do not exist. The searches have so far covered only a small fraction of the total “parameter space”—that is, the combination of target stars, radio frequencies, power levels and temporal coverage that observers must scan before drawing a definitive conclusion. Nevertheless, initial results are already beginning to place some interesting limits on the prevalence of radio-transmitting civilizations in the galaxy [see box on next page].

The Fermi Paradox becomes evident when one examines

some of the assumptions underlying SETI, especially the total number of galactic civilizations, both extant and extinct, that it implicitly assumes. One of the current leaders of the field, Paul Horowitz of Harvard University, has stated that he expects at least one radio-transmitting civilization to reside within 1,000 light-years of the sun, a volume of space that contains roughly a million solar-type stars. If so, something like 1,000 civilizations should inhabit the galaxy as a whole.

This is rather a large number, and unless these civilizations are very long-lived, it implies that a truly enormous number must have risen and fallen over

the course of galactic history. (If they are indeed long-lived—if they manage to avoid natural or self-induced catastrophes and to remain detectable with our instruments—that raises other problems, as discussed below.) Statistically, the number of civilizations present at any one time is equal to their rate of formation multiplied by their mean lifetime. One can approximate the formation rate as the total number that have ever appeared divided by the age of the galaxy, roughly 12 billion years. If civilizations form at a constant rate and live an average of 1,000 years each, a total of 12 billion or so technological civilizations must have existed over the

history of the galaxy for 1,000 to be extant today. Different assumptions for the formation rate and average lifetime yield different estimates of the number of civilizations, but all are very large numbers. This is what makes the Fermi Paradox so poignant. Would none of these billions of civilizations, not even a single one, have left any evidence of their existence?

Extraterrestrial Migration

This problem was first discussed in detail by astronomer Michael H. Hart and engineer David Viewing in independent papers, both published in

Where They Could Hide

The galaxy appears to be devoid of supercivilizations, but lesser cultures could have eluded the ongoing searches

by Andrew J. LePage

No SETI program has ever found a verifiable alien radio signal. What does that null result mean? Any answer must be highly qualified, because the searches have been so incomplete. Nevertheless, researchers can draw some preliminary conclusions about the number and technological sophistication of other civilizations.

The most thoroughly examined frequency channel to date, around 1.42 gigahertz, corresponds to the emission line of the most common element in the universe, hydrogen—on the premise that if extraterrestrials had to pick some frequency to attract our attention, this would be a natural choice. The diagram on the opposite page, the first of its kind, shows exactly how thoroughly the universe has been searched for signals at or near this frequency. No signal has ever been detected, which means that any civilizations either are out of range or do not transmit with enough power to register on our instruments. The null results therefore rule out certain types of civilizations, including primitive ones close to Earth and advanced ones farther away.

The chart quantifies this conclusion. The horizontal axis shows the distance from Earth. The vertical axis gives the effective

isotropic radiated power (EIRP) of the transmitters. The EIRP is essentially the transmitter power divided by the fraction of the sky the antenna covers. In the case of an omnidirectional transmitter, the EIRP is equal to the transmitter power itself. The most powerful on this planet is currently the Arecibo radio telescope in Puerto Rico, which could be used as a narrowly beamed radar system with an EIRP of nearly 10^{14} watts.

The EIRP can serve as a crude proxy for the technological level of an advanced civilization, according to a scheme devised by Russian SETI pioneer Nikolai S. Kardashev in the early 1960s and later extended by Carl Sagan. Type I civilizations could transmit signals with a power equivalent to all the sunlight striking an Earth-like planet, about 10^{16} watts. Type II civilizations could harness the entire power output of a sunlike star, about 10^{27} watts. Still mightier type III civilizations command an entire galaxy, about 10^{38} watts. If the capability of a civilization falls in between these values, its type is interpolated logarithmically. For example, based on the Arecibo output, humanity rates as a type 0.7 civilization.

For any combination of distance and transmitter power, the diagram indicates

what fraction of stars has been scanned so far without success. The white and colored areas represent the civilizations whose existence we therefore can rule out with varying degrees of confidence. The black area represents civilizations that could have evaded the searches. The size of the black area increases toward the right—that is, going farther away from Earth. SETI programs completely exclude Arecibo-level radio transmissions out to 50 or so light-years. Farther away, they can rule out the most powerful transmitters. Far beyond the Milky Way, SETI fails altogether, because the relative motions of galaxies would shift any signals out of the detection band.

These are not trivial results. Before scientists began to look, they thought that type II or III civilizations might actually be quite common. That does not appear to be the case. This conclusion agrees with other astronomical data. Unless supercivilizations have miraculously repealed the second law of thermodynamics, they would need to dump their waste heat, which would show up at infrared wavelengths. Yet searches performed by Jun Jugaku of the Research Institute of Civilization in Japan and his colleagues have seen no such offal out to a distance of about 80 light-years. Assuming that civilizations are scattered randomly, these findings also put limits on the average spacing of civilizations and thus on their inferred prevalence in unprobed areas of the galaxy.

On the other hand, millions of undetected civilizations only slightly more advanced than our own could fill the Milky Way. A hundred or more type I civilizations could also share the galaxy with us. To complicate matters further, extraterres-

1975. It was later extended by various researchers, most notably physicist Frank J. Tipler and radio astronomer Ronald N. Bracewell. All have taken as their starting point the lack of clear evidence for extraterrestrial visits to Earth. Whatever one thinks about UFOs, we can be sure that Earth has not been taken over by an extraterrestrial civilization, as this would have put an end to our own evolution and we would not be here today.

There are only four conceivable ways of reconciling the absence of ETs with the widely held view that advanced civilizations are common. Perhaps interstellar spaceflight is infeasible, in which case ETs could never have come here

even if they had wanted to. Perhaps ET civilizations are indeed actively exploring the galaxy but have not reached us yet. Perhaps interstellar travel is feasible, but ETs choose not to undertake it. Or perhaps ETs have been, or still are, active in Earth's vicinity but have decided not to interfere with us. If we can eliminate each of these explanations of the Fermi Paradox, we will have to face the possibility that we are the most advanced life-forms in the galaxy.

The first explanation clearly fails. No known principle of physics or engineering rules out interstellar spaceflight. Even in these early days of the space age, engineers have envisaged propulsion

strategies that might reach 10 to 20 percent of the speed of light, thereby permitting travel to nearby stars in a matter of decades [see "Reaching for the Stars," by Stephanie D. Leifer; *SCIENTIFIC AMERICAN*, February 1999].

For the same reason, the second explanation is problematic as well. Any civilization with advanced rocket technology would be able to colonize the entire galaxy on a cosmically short timescale. For example, consider a civilization that sends colonists to a few of the planetary systems closest to it. After those colonies have established themselves, they send out secondary colonies of their own, and so on. The number of colonies grows exponentially. A colonization wave front will move outward with a speed determined by the speed of the starships and by the time required by each colony to establish itself. New settlements will quickly fill in the volume of space behind this wave front [see illustration on next page].

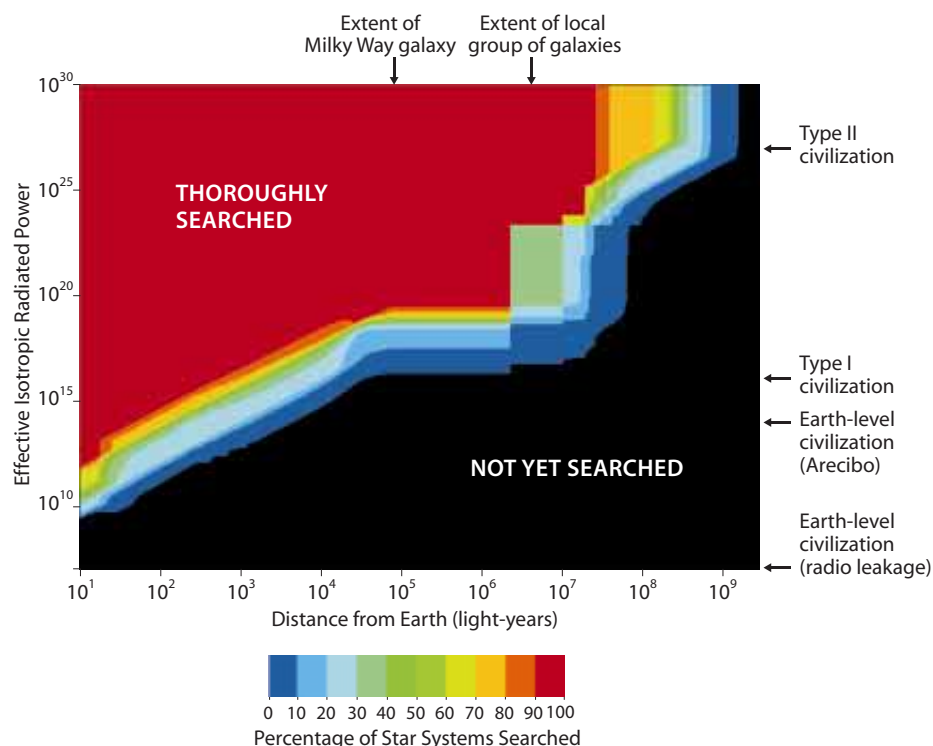
Assuming a typical colony spacing of 10 light-years, a ship speed of 10 percent that of light, and a period of 400 years between the foundation of a colony and its sending out colonies of its own, the colonization wave front will expand at an average speed of 0.02 light-year a year. As the galaxy is 100,000 light-years across, it takes no more than about five million years to colonize it completely. Though a long time in human terms, this is only 0.05 percent of the age of the galaxy. Compared with the other relevant astronomical and biological timescales, it is essentially instantaneous. The greatest uncertainty is the time required for a colony to establish itself and spawn new settlements. A reasonable upper limit might be 5,000 years, the time it has taken human civilization to develop from the earliest cities to spaceflight. In that case, full galactic colonization would take about 50 million years.

The implication is clear: the first technological civilization with the ability and the inclination to colonize the galaxy could have done so before any competitors even had a chance to evolve. In principle, this could have happened billions of years ago, when Earth was inhabited solely by microorganisms and was wide open to interference from outside. Yet no physical artifact, no chemical traces, no obvious biological influence indicates that it has ever been intruded upon. Even if Earth was deliberately seeded with life, as some scientists have speculated, it has been left alone since then.

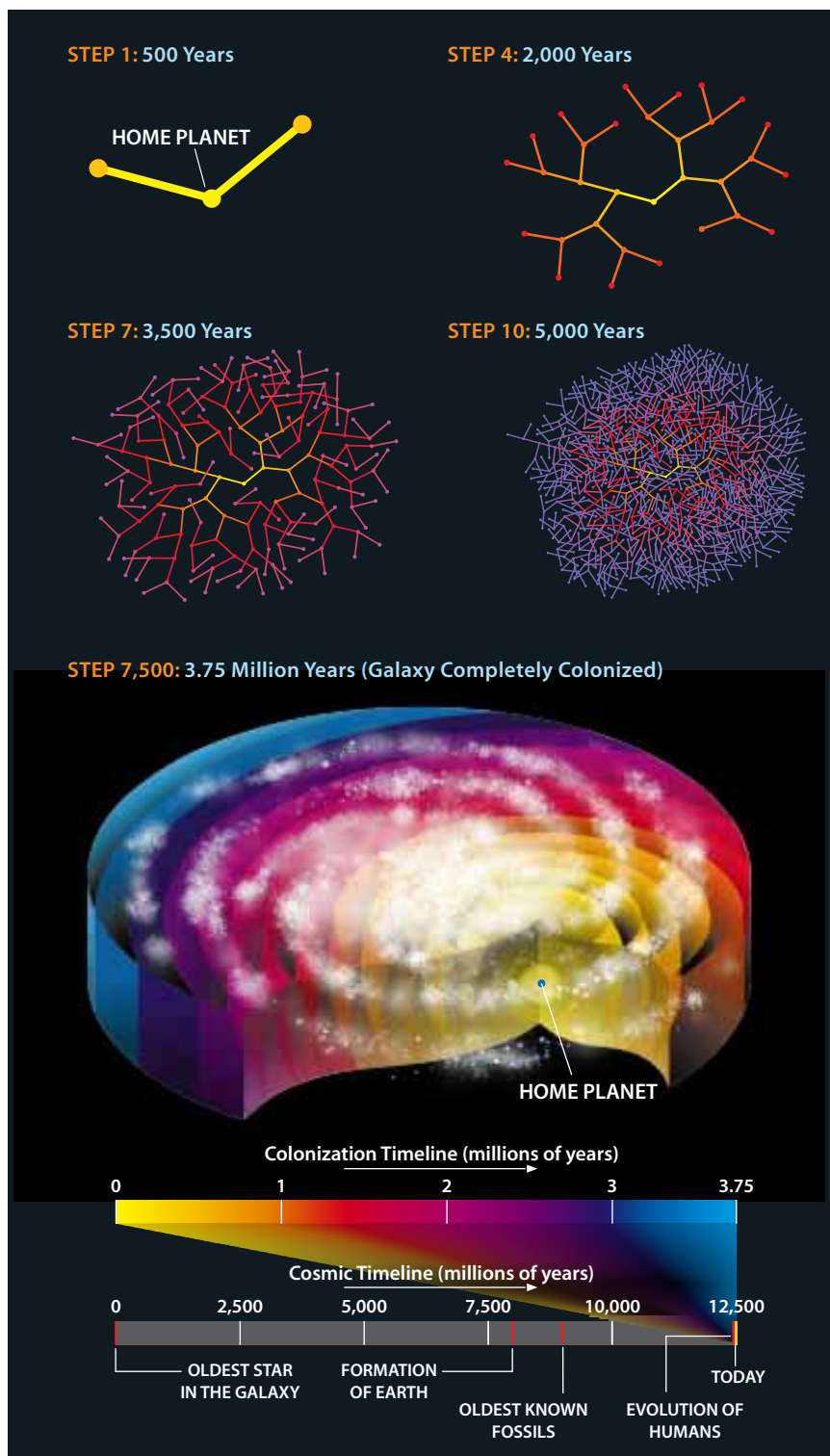
trials might be using another frequency or transmitting sporadically. Indeed, SETI programs have logged numerous "extrastatistical events," signals too strong to be noise but never reobserved. Such transmissions might have been wayward radio waves from nearby cell phones—or they might have been intermittent extraterrestrial broadcasts. No one yet knows. Although the cut-

ting edge of technology has made SETI ever more powerful, we have explored only a mere fraction of the possibilities.

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RESULTS OF SETI PROGRAMS are summarized in this diagram. The black area shows which civilizations could have eluded our radio searches, either because they are too far away or because their transmitters are too weak. To make sense of this diagram, choose a transmitter strength (vertical axis), read across to the edge of the black area and go down to find the distance from Earth (horizontal axis). For example, an Arecibo-class transmitter of 10^{14} watts must be farther away than about 4,000 light-years to have eluded the searches altogether. The color code provides more detailed information—namely, the estimated percentage of all star systems that have been examined for transmitters of a given power or greater.



COLONIZATION OF THE GALAXY

is not as time-consuming as one might think. Humans could begin the process by sending colonists to two nearby stars, a trip that might take 100 years with foreseeable technology. After 400 years to dig in, each colony sends out two of its own, and so on. Within 10,000 years our descendants could inhabit every star system within 200 light-years. Settling the entire galaxy would take 3.75 million years—a split second in cosmic terms. If even one alien civilization has ever undertaken such a program, its colonies should be everywhere we look.

existence, or agree on the same set of ethical rules for the treatment of less developed forms of life. It would take only one technological civilization to embark, for whatever reason, on a program of galactic colonization. Indeed, the only technological civilization we actually know anything about—namely, our own—has yet to self-destruct, shows every sign of being expansionist, and is not especially reticent about interfering with other living things.

Despite the vastness of the endeavor, I think we can identify a number of reasons why a program of interstellar colonization is actually quite likely. For one, a species with a propensity to colonize would enjoy evolutionary advantages on its home planet, and it is not difficult to imagine this biological inheritance being carried over into a space-age culture. Moreover, colonization might be undertaken for political, religious or scientific reasons. The last seems especially probable if we consider that the first civilization to evolve would, by definition, be alone in the galaxy. All its SETI searches would prove negative, and it might initiate a program of systematic interstellar exploration to find out why.

Resolving the Paradox?

Furthermore, no matter how peaceable, sedentary or uninquisitive most ET civilizations may be, ultimately they will all have a motive for interstellar migration, because no star lasts forever. Over the history of the galaxy, hundreds of millions of solar-type stars have run out of hydrogen fuel and ended their days as red giants and white dwarfs. If civilizations were common around such stars, where have they gone? Did they all just allow themselves to become extinct?

The apparent rarity of technological civilizations begs for an explanation. One

It follows that any attempt to resolve the Fermi Paradox must rely on assumptions about the behavior of other civilizations. For example, they might destroy themselves first, they might have no interest in colonizing the galaxy, or they might have strong ethical codes against interfering with primitive life-forms. Many SETI researchers, as well as others who are convinced that ET civilizations must be common, tend to dismiss

the implications of the Fermi Paradox by an uncritical appeal to one or more of these sociological considerations.

But they face a fundamental problem. These attempted explanations are plausible only if the number of extraterrestrial civilizations is small. If the galaxy has contained millions or billions of technological civilizations, it seems very unlikely that they would all destroy themselves, be content with a sedentary

possibility arises from considering the chemical enrichment of the galaxy. All life on Earth, and indeed any conceivable extraterrestrial biochemistry, depends on elements heavier than hydrogen and helium—principally, carbon, nitrogen and oxygen. These elements, produced by nuclear reactions in stars, have gradually accumulated in the interstellar medium from which new stars and planets form. In the past the concentrations of these elements were lower—possibly too low to permit life to arise. Among stars in our part of the galaxy, the sun has a relatively high abundance of these elements for its age. Perhaps our solar system had a fortuitous head start in the origins and evolution of life.

But this argument is not as compelling as it may at first appear. For one, researchers do not know the critical threshold of heavy-element abundances that life requires. If abundances as low as a tenth of the solar value suffice, as seems plausible, then life could have arisen around much older stars. And although the sun does have a relatively high abundance of heavy elements for its age, it is certainly not unique [see “Here Come the Suns,” by George Musser; *SCIENTIFIC AMERICAN*, May 1999]. Consider the nearby sunlike star 47 Ursae Majoris, one of the stars around which a Jupiter-mass planet has recently been discovered. This star has the same element abundances as the sun, but its estimated age is seven billion years. Any life that may have arisen in its planetary system should have had a 2.5-billion-year head start on us. Many millions of similarly old and chemically rich stars populate the galaxy, especially toward the center. Thus, the chemical evolution of the galaxy is almost certainly not able to fully account for the Fermi Paradox.

To my mind, the history of life on Earth suggests a more convincing explanation. Living things have existed here almost from the beginning, but multicellular animal life did not appear until about 700 million years ago. For more than three billion years, Earth was inhabited solely by single-celled microorganisms. This time lag seems to imply that the evolution of anything more complicated than a single cell is unlikely. Thus, the transition to multicelled animals might occur on only a tiny fraction of the millions of planets that are inhabited by single-celled organisms.

It could be argued that the long solitude of the bacteria was simply a necessary precursor to the eventual appear-

ance of animal life on Earth. Perhaps it took this long—and will take a comparable length of time on other inhabited planets—for bacterial photosynthesis to produce the quantities of atmospheric oxygen required by more complex forms of life. But even if multicelled life-forms do eventually arise on all life-bearing planets, it still does not follow that these will inevitably lead to intelligent creatures, still less to technological civilizations. As pointed out by Stephen Jay Gould in his book *Wonderful Life*, the evolution of intelligent life depends on a host of essentially random environmental influences.

This contingency is illustrated most clearly by the fate of the dinosaurs. They dominated this planet for 140 million years yet never developed a technological civilization. Without their extinction, the result of a chance event, evolutionary history would have been very different. The evolution of intelligent life on Earth has rested on a large number of chance events, at least some of which had a very low probability. In 1983 physicist Brandon Carter concluded that “civilizations comparable with our own are likely to be exceedingly rare, even if locations as favorable as our own are of common occurrence in the galaxy.”

Of course, all these arguments, though in my view persuasive, may turn out to be wide of the mark. In 1853 William Whewell, a prominent protagonist in the extraterrestrial-life debate, observed, “The discussions in which we are engaged belong to the very boundary regions of science, to the frontier where knowledge ... ends and ignorance begins.” In spite of all the advances since Whewell’s day, we are in basically the same position today. And the only way to lessen our ignorance is to explore our cosmic surroundings in greater detail.

That means we should continue the SETI programs until either we detect signals or, more likely in my view, we can place tight limits on the number of radio-transmitting civilizations that may have escaped our attention. We should pursue a rigorous program of Mars exploration with the aim of determining whether or not life ever evolved on that planet and, if not, why not. We should press ahead with the development of large space-based instruments capable of detecting Earth-size planets around nearby stars and making spectroscopic searches for signs of life in their atmospheres. And eventually we should develop technologies for interstellar space



STELLAR CORPSES, such as the Butterfly Nebula, litter the galaxy. If intelligent beings used to live around these stars, where are they now?

probes to study the planets around nearby stars.

Only by undertaking such an energetic program of exploration will we reach a fuller understanding of our place in the cosmic scheme of things. If we find no evidence for other technological civilizations, it may become *our* destiny to embark on the exploration and colonization of the galaxy. SA

The Author

IAN CRAWFORD is an astronomer in the department of physics and astronomy at University College London. His research interests mostly concern the study of interstellar and circumstellar environments, including circumstellar disks thought to be forming planets. He believes that the cosmic perspective provided by the exploration of the universe argues for the political unification of our world. He explains: “This perspective is already apparent in images of Earth taken from space, which emphasize the cosmic insignificance of our entire planet, never mind the national boundaries we have drawn upon its surface. And if we do ever meet other intelligent species out there among the stars, would it not be best for humanity to speak with a united voice?”

Intragalactically Speaking

The vastness and vagaries of space will force interstellar correspondents into extreme measures

by George W. Swenson, Jr.

Among our galaxy's 100 billion or more stars there may be thousands of advanced civilizations, some scientists suspect—a possibility supported by recent evidence indicating that planetary systems are more common in the Milky Way than was previously thought. For four decades, researchers have sporadically scanned the heavens for any radio signals that an advanced civilization may have emitted into the vastness of the galaxy. This search for extraterrestrial intelligence (SETI) is a passive pursuit, based on the use of dish antennas and sensitive radio receivers to pull in signals that, if they are out there, are probably quite weak by the time they get to us.

Essentially all major SETI programs here on Earth have been based on attempts to receive signals that would have been transmitted decades or, in all probability, centuries or millennia ago. For this reason, little has been published on the complementary problem of SETI, which could be phrased as follows: What would it take to build a radio-transmitting system that would have even the slightest chance of being detected by a receiver tens or hundreds of light-years away?

The exercise is not a mere abstraction—as SETI specialists have long realized, it would be impossible to mount a credible search and receiving effort without having some ideas about the transmission system and strategy that would most likely be used on the other end. Perhaps most important, a step-by-step accounting of the difficulties of beaming a signal over such enormous distances reveals one of SETI's most fundamental concerns: why basic physics indicates that it will be extremely difficult for any civilization to announce its presence

to another such civilization in an indeterminate solar system among the galaxy's huge profusion of stars.

This analysis—along with theories that advanced civilizations may be far rarer than some scientists believe [see “Where Are They?” by Ian Crawford, on page 38]—could shed light on the central paradox of SETI: if thousands of advanced civilizations exist throughout our own Milky Way galaxy, why haven't we heard from any of them?

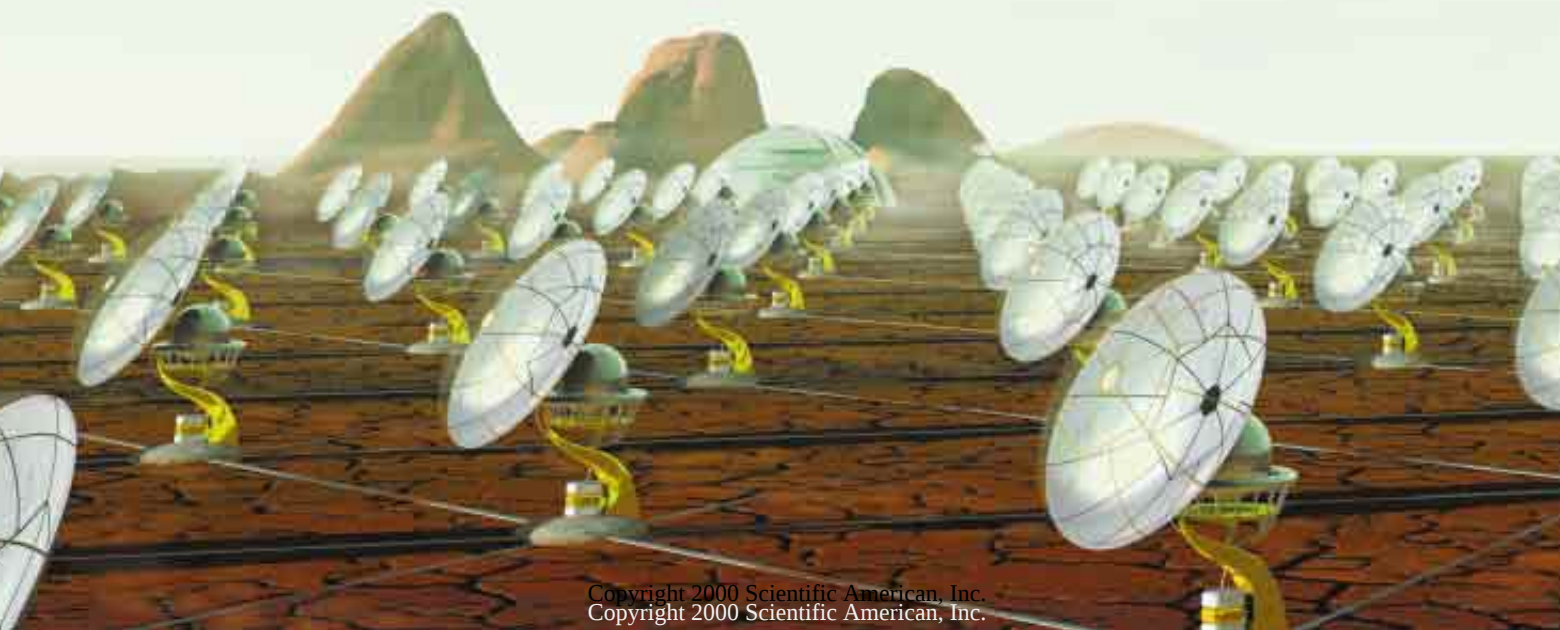
Being Heard above the Din

The first major task in designing a transmitter capable of sending a signal off into the galaxy is choosing the part of the electromagnetic spectrum that will carry the signal. To keep the scope of this article manageable, I'll choose radio waves. They travel through interstellar space quite well in comparison with some other forms of electromagnetic radiation, such as light, which suffer from, among other factors, scattering and absorption by interstellar dust.

Within the radio spectrum, SETI specialists have settled on a range of frequencies between 1 and 3 gigahertz as being the most likely for interstellar communication. Our engineering techniques are quite advanced in this part of the spectrum. Also, with the exception of emissions from neutral hydrogen in the vicinity of 1.42 gigahertz, absorption and obscuration of waves by interstellar molecules and dust clouds is relatively minimal at these frequencies, as is background radiation from the Milky Way.

Radio emissions move through space in the form of period-

PAT RAWLINGS



ically varying electric and magnetic fields. The fields travel together at the speed of light, 300,000 kilometers per second. The distance at which a radio wave can be detected depends on five major factors (assuming that the transmitting and receiving antennas have been well designed): the electromagnetic noise environment of the receiver, the sensitivity of the receiver, the power of the transmitted signal, and the size of the transmitting and receiving antennas.

Let's begin with the noise: it is literally everywhere. Electromagnetic radiation can be coherent—that is, regularly structured, like the emissions of a radio transmitter. Alternatively, it can be incoherent, consisting of random impulses such as the hiss you hear from a radio receiver with no station tuned in. That incoherent radiation is known as noise.

Every material body at a temperature above absolute zero emits electromagnetic radiation—noise—throughout the spectrum, its frequency of maximum intensity being determined by its absolute temperature. For convenience, physicists sometimes characterize this noise by the temperature of an imaginary “black body” representing the sources of noise in, for example, a communications system.

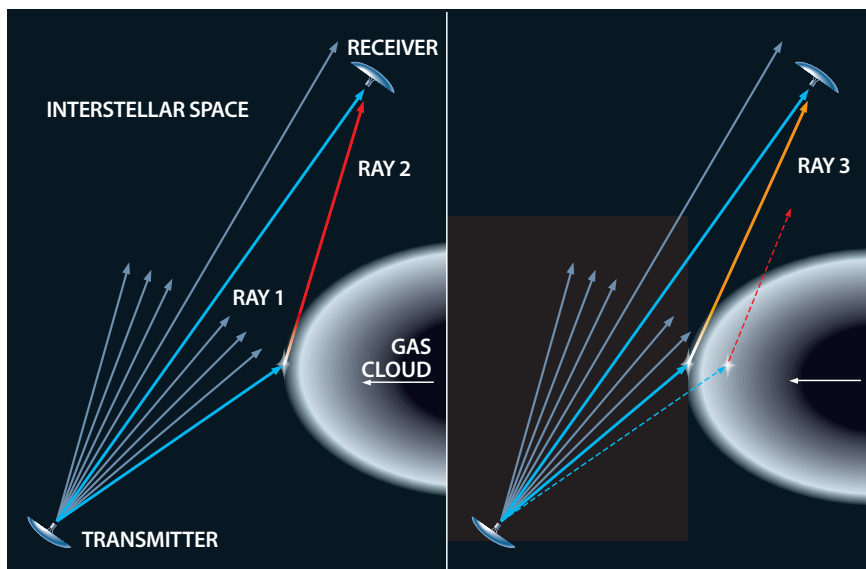
This system noise fundamentally limits our ability to communicate. To receive a signal, its power at the receiving antenna must be at least close to that of the noise at the antenna. An analogous situation involves two people attempting to converse at a boisterous party: they have to raise their voices to a level at which they can compete with the noise around them.

The noise in a radio receiver's amplifier chain comes from two sources: externally, from the antenna, and internally, generated within the amplifiers themselves. Amplifier technology has advanced to the point where it is possible to build a receiver that has internally generated noise of only a few kelvins.

The noise from the external environment is generally beyond the control of the operator, so it dominates the performance of a high-quality receiving system, such as the ones used in astronomy. External noise sources include the ground (for antennas built on a planet), the planetary atmosphere, the galactic background, astronomical sources of radio emissions inside and outside the galaxy, and the cosmic background radiation, the remnant of the big bang that initiated our universe. On Earth, for a receiver at or slightly beyond the current state of the art, all these sources, including the internal noise generated in the receiver, add up to about 15 kelvins in a system shielded to minimize the radiation from the ground.

EXTRATERRESTRIAL RADIO OPERATOR (*above*) might control an array of parabolic “dish” antennas with a large effective area.





MULTIPATH EFFECTS result when an interstellar gas cloud refracts, or bends, a ray (red and orange) so that it coincides at the receiver with another ray (blue) from the same transmitter. As the cloud moves, the difference in path lengths between the direct and refracted rays changes. Thus, the received rays cycle back and forth between constructive reinforcement and cancellation, causing the received signal—the sum of the rays—to scintillate.

How much power must we deliver to the distant receiving antenna to overcome this noise temperature? To calculate that value, we first note that the noise power in the receiver depends on the frequency range, also known as bandwidth, of the receiver. Because noise is distributed across the spectrum, the narrower the receiver bandwidth, the less noise power that is admitted to the receiver. Thus, in order to detect the weakest possible signal, the bandwidth should be restricted to the smallest value that will accommodate the anticipated signal.

On the other hand, the more bandwidth, the higher the rate at which we can send data. For example, normal speech requires about 2.5 kilohertz, and a standard television signal occupies about 4.5 megahertz.

Let's settle on an information rate of five bits per second. Depending on the relative amounts of signal and noise, that will require a bandwidth of about 2.5 hertz. This bandwidth will let us send the message "hello" in five seconds, assuming that five bits are needed to represent each character.

Now that we have a specific bandwidth and noise temperature, we can address our earlier question: How much signal power is needed at the receiving antenna to overcome the noise power? The formula to compute the noise power (P_n) is $P_n = kTB$, where k is Boltzmann's constant, 1.3806×10^{-23} joule per kelvin; T is the noise temperature, 15 kel-

vins; and B is the bandwidth of the detecting system, 2.5 hertz. Performing the calculation, the system noise power is 5.2×10^{-22} watt, and the receiver would need a signal power from the distant transmitter equal to this value, or nearly so, in order to detect it in the presence of that noise. We will assume for now that the receiving antenna has an effective area of one square meter. Thus, the required intensity of the signal at the receiving antenna is 5.2×10^{-22} watt per square meter.

The power needed from our distant transmitter to deliver this intensity to the receiving antenna depends on how far away we are. It also depends on whether we are transmitting the signal in all directions, more or less, at once ("omnidirectionally") or beaming it in a narrow cone. For the distance, let us arbitrarily pick 100 light-years, which equals 9.46×10^{17} meters. For the transmission mode, let's assume we are radiating the signal omnidirectionally, because we do not know where our putative correspondent is.

Applying the inverse-square relation, we can calculate the power required from a transmitter radiating omnidirectionally at that distance. It is $(5.2 \times 10^{-22}) \times 4\pi \times (9.46 \times 10^{17})^2 = 5.8 \times 10^{15}$ watts. That is, of course, an implausibly large power requirement; for comparison, it is more than 7,000 times the total electricity-generating capacity of the U.S.

Moreover, in galactic terms, 100 light-

years is a minuscule distance. Within this distance of Earth there are on the order of 1,000 stars—or less than a millionth of 1 percent of the stars in the galaxy. To have a reasonable chance of happening on an advanced civilization, we would have to reach the stars within a far greater volume.

Is Beaming Better?

As an alternative to omnidirectional transmission and reception, beamed signals may prove more encouraging. In particular, let's consider the trade-off between receiving-antenna size and the signal power required from the transmitter. A receiving antenna whose effective area is very large in comparison with the square of the wavelength it is receiving has a narrow receiving "beam." When such an antenna is aimed at a transmitter, it has a large "gain" in the amount of power extracted from the radio wave. In this case, less power is needed to transmit to the receiver. The disadvantage—that the receiving beam must be aimed in a specific direction—is significant in our case, because we are assuming that any would-be correspondents do not know where we are.

Nevertheless, let's look at the numbers. We had assumed in our previous example that the receiving antenna had an effective area of only one square meter. The unit might be a horn-type antenna or a parabolic "dish" with a diameter of about 1.5 meters. Such an antenna, operating at a wavelength of 20 centimeters, would have a reception "beam" of about 11 degrees, within which a signal would be efficiently received when it was pointing at the transmitter.

Even larger receiving antennas would reduce the transmitter power requirements still further but, again, at a price—a narrower beam. Relative to a hypothetical omnidirectional antenna, the gain represented by a beamed signal is proportional to the antenna's effective area in square wavelengths. Take as an example an array of contiguous antennas one kilometer on a side. At a wavelength of 20 centimeters, this array would have a gain one million times greater than the one-square-meter antenna. It is a pity, though, that it would also have a beamwidth of only 11 thousandths of a degree. The transmitter power required would be reduced a million times, but the narrow beam would require fantastically precise pointing and tracking.

If we employ a similar one-kilometer-

square antenna array to transmit our signal, we obtain a similar gain improvement—and beamwidth reduction—as in the receiving case. Suppose there were one-kilometer-square antenna arrays on each end of our communications channel. In this case, the required transmitter power would be only 5,700 watts. It is rather unlikely, however, that the very narrow beams of each of these antennas would ever fortuitously line up with one another.

It is a classic trade-off: with minimal antenna areas the required transmitting power greatly exceeds the generating capacity of the world. With mammoth antennas, on the other hand, the power requirements are modest, but the transmitting and receiving beams are so narrow it would be almost impossible for the would-be correspondents to find one another in the unfathomably large volumes of galactic space.

There are, of course, many compromises among the extreme examples given above. Unfortunately, none promises relief from the basic fact of interstellar communication: the great distances involved require extreme measures.

Still, it is not quite time to give up hope. The communications system parameters we have chosen, though reasonable, are still somewhat arbitrary. We could, for instance, make other assumptions about the distant correspondent's technology, allowing us to adopt a lower signal-to-noise ratio or a narrower bandwidth, which would reduce the power requirements.

More important, a very large receiving antenna, in the form of an aggregated array of individual antennas and receivers, can be programmed to produce many simultaneous receiving beams in different directions, thus expediting the search for an unknown transmitter. Similarly, we could employ many receiving frequency channels simultaneously—a technique used in current SETI programs. These multiplexing advantages cannot be applied to transmission, however, without reductions in the power available to each beam or each frequency channel, because the total power is fixed.

Penetrating the Medium

So far we have discussed only the most elementary design considerations involving the two ends—transmitter and receiver—of an interstellar communications system. The great space in between

also presents difficulties, such as so-called multipath effects. To understand these effects, it is necessary to know something about the way in which radio waves propagate. In a vacuum, they will travel in a straight line unless they encounter a material obstacle that absorbs, reflects or refracts them. It so happens that interstellar space contains material, such as gases and particles at low concentrations, as well as quasi-static magnetic fields. Over the enormous distances involved, these can divert radio waves from straight paths, change polarization and produce sporadic fluctuations in received signal strength. Such phenomena militate against the use of very narrow transmitting or receiving beams—thus exacerbating the transmitting-power requirement.

Refraction occurs when the waves enter a gas, say, in which their velocity differs from that in free space. Refraction changes the direction of the waves and can cause two waves originating at the same source to add together to produce a more complex wave. For example, as the wave enters the gas, part of it may be slowed more than another, depending on the distribution of the gas. The variation in velocity could cause a phase shift between components of the resulting wave. Depending on the magnitude of the phase shift and the difference in path length between the wave's components, phase-shifted portions could reinforce each other, or cancel each other, or anything in between.

Now suppose that the patch of gas in

the path of the second wave is moving relative to the wave path, so that the phase shift varies with time [see *illustration on opposite page*]. In this case, the aggregate of the two wave components will vary with time, reinforcing itself or canceling itself out at intervals. Similar effects can be produced by many different situations involving reflecting objects, Doppler shifts and multiple wave paths. Such examples of multipath propagation can convert a steady signal as emitted from a transmitter into a strongly modulated signal as detected by a far-off receiver.

As this analysis suggests, the use of radio waves as a medium for making interstellar contact is discouraging. The galaxy's enormous distances inevitably require fantastic measures—stunningly high transmitter power or huge antennas and impractically narrow beams. Certainly the kind of systems that would be needed to mount a realistic project to beam a signal to a large sampling of stars are probably beyond the resources of a society like that of Earth. Furthermore, even if contact could somehow be made, the time delay before a response to a message could be received might very well stretch into many centuries. Even if the formidable physical constraints could be overcome, this is clearly a project for many generations in succession. In all likelihood, it will require an enduring organization based on immutable dogma—like one of the world's major religions.

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The Author

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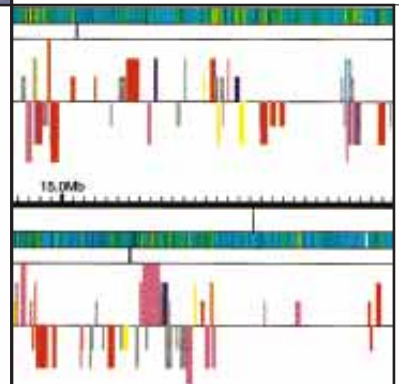
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THE BUILDING OF THE HUMAN GENOME



SINCESS

What a difference a decade makes. Time was when politicians—not to mention the general public—didn't know a genome from those diminutive forest-dwelling fellows of folklore. In 1989, for instance, President George Bush made a genome-related gaffe in a story I've been dining out on ever since.

In a ceremony in the East Room of the White House to award the National Medals of Science and Technology, Bush proudly recounted the things the Reagan and Bush administrations had done for science: the space station, the (now defunct) Superconducting Super Collider and the Human “*Gnome*” Initiative. He made no attempt to correct himself. Not a titter nor a murmur could be heard; the audience—for the most part, top science bureaucrats and captains of technology industries—didn't even exchange surprised looks. With appropriate gravitas, the award recipients—which, ironically, included Stanley N. Cohen and Herbert W. Boyer, the inventors of gene splicing—stepped up to the podium to shake hands with the president and accept their honors.

Had I heard correctly? Evidently so—at the post-award reception, the room was abuzz as people commented on Bush's mistake and regretfully interpreted it as a sign of his ignorance about the Human Genome Project. But to make sure, when I got back to my office I called the White House media office to get a copy of what Bush had been reading from as well as a copy of the official transcript. The first clearly said “genome”; the second said “gnome.” This in a year when the National Institutes of Health would spend \$28.2 million on the early stages of the Human Genome Project.

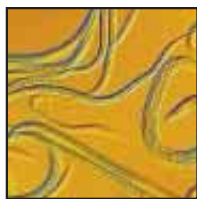
Today the genome project is essentially complete, and few people can say they've never heard of it. Indeed, many have invested in genome-related technologies, which have burgeoned into a multibillion-dollar industry. In the following special report, *SCIENTIFIC AMERICAN* brings readers up to date on the state of genomics and introduces two new fields—bioinformatics and proteomics—that are poised to harvest the fruits of deciphering the human genome.

After reading these pages, let no one confuse the human genome with a tacky yard ornament ever again.

—Carol Ezzell, staff writer

JULIO E. CELIS (Danish Center for Human Genome Research, Aarhus, left); JEFF JOHNSON (center);
SCIENCE, VOL. 287, NO. 5461, MARCH 24, 2000 (right); LAURIE GRACE (border)

THE HUMAN GENOME BUSINESS TODAY



by Kathryn Brown

It's been a wild ride for the corporate and government parties who have deciphered the human genetic code. The fun has just begun

By the time this magazine hits your mailbox, you'll be able to read the entire genetic code of a human being over the Internet. It's not exactly light reading—start to finish, it's nothing but the letters A, T, C and G, repeated over and over in varying order, long enough to fill more than 200 telephone books. For biologists, though, this code is a runaway best-seller. The letters stand for the DNA chemicals that make up all your genes, influencing the way you walk, talk, think and sleep. "We're talking about reading your own instruction book," marvels Francis S. Collins, director of the National Human Genome Research Institute in Bethesda, Md. "What could be more compelling than that?"

Collins heads the Human Genome Project (HGP), so far a \$250-million effort to write out the map of all our genes. The HGP is a publicly funded consortium that includes four large sequencing centers in the U.S., as well as the Sanger Center near Cambridge, England, and labs in Japan, France, Germany and China. Working together for more than a decade, over 1,100 scientists have crafted a map of the three billion DNA base pairs, or units, that make up the human genome. And they are not alone. In April a brash young company called Celera Genomics in Rockville, Md., beat the public consor-

tium to the punch, announcing its own rough draft of the human genome. The rivalry has cast a spotlight on the human genetic code—and what, exactly, researchers now plan to do with it.

"For a long time, there was a big misconception that when the DNA sequencing was done, we'd have total enlightenment about who we are, why we get sick and why we get old," remarks geneticist Richard K. Wilson of Washington University, one partner in the public consortium. "Well, total enlightenment is decades away."

But scientists can now imagine what that day looks like. Drug companies, for instance, are collecting the genetic know-how to make medicines tailored to specific genes—an effort called pharmacogenomics. In the years to come, your pharmacist may hand you one version of a blood pressure drug, based on your unique genetic profile, while the guy in line behind you gets a different version of the same medicine. Other companies are already cranking out blood tests that reveal telltale disease-gene mutations—and forecast your chances of coming down with conditions such as Huntington's disease. And some scientists still hold out hope for gene therapy: directly adding healthy genes to a patient's body. "Knowing the genome will change the way drug trials are done and kick off a whole new era of individualized medicine," predicts J. Craig Venter, president of Celera.

Even with the human code in hand, however, the genomics industry faces challenges. Some are technical: it's one thing to know a gene's chemical structure, for instance, but quite another to understand its actual function. Other challenges are legal: How much must you know about a gene in order to patent it? And finally, many dilemmas are social: Do you really want to be diagnosed with a disease that can't be treated—and won't affect you for another 20 years? As scientists begin unraveling the genome, the endeavor may come to seem increasingly, well, human.

The "Race"

This spring all eyes were on the first finish line in the genome: a rough-draft sequence of the 100,000 or so genes inside us all. The HGP's approach has been described as painstaking and precise. Beginning with blood and sperm cells, the team separated out the 23 pairs of chromosomes that hold human genes. Scientists then clipped bits of DNA from every chromosome, identified the sequence of DNA bases in each bit, and, finally, matched each snippet up to the DNA on either side of it in the chromosome. And on they went, gradually crafting the sequences for individual gene segments, complete genes, whole chromosomes and, eventually, the entire genome. Wilson compares this approach to taking out one



CELERA GENOMICS's gene-sequencing factory in Rockville, Md., has 300 automated DNA sequencers—as well as a nifty blue DNA helix on the ceiling.

page of an encyclopedia at a time, ripping it up and putting it together again.

In contrast, Celera took a shorter route: shredding the encyclopedia all at once. Celera's so-called shotgun sequencing strategy tears all the genes into fragments simultaneously and then relies on computers to build the fragments into a whole genome. "The emphasis is on computational power, using algorithms to sequence the data," says J. Paul Gilman, Celera's director of policy planning. "The advantage is efficiency and speed."

The HGP and Celera teams disagree over what makes a "finished genome." This spring Celera announced that it had finished sequencing the rough-draft genome of one anonymous person and that it would sort the data into a map in just six weeks. But the public team immediately cried foul, as Collins noted that Celera fell far short of its original genome-sequencing goals. In 1998, when the company began, Celera scientists planned to sequence the full genomes of several people, checking its "consensus"

genome 10 times over. In its April announcement, however, Celera declared that its rough genome sequencing was complete with just one person's genome, sequenced only three times.

Although many news accounts have characterized the HGP and Celera as competing in a race, the company has had a decided advantage. Because the HGP is a public project, the team routinely dumps all its genome data into GenBank, a public database available through the Internet (at www.ncbi.nlm.nih.gov/). Like everyone else, Celera has used that data—in its case, to help check and fill the gaps in the company's rough-draft genome. Essentially Celera used the public genome data to stay one step ahead in the sequencing effort. "It does stick in one's craw a bit," Wilson remarks. But Gilman asserts that Celera's revised plan simply makes good business sense. "The point is not just to sit around and sequence for the rest of our

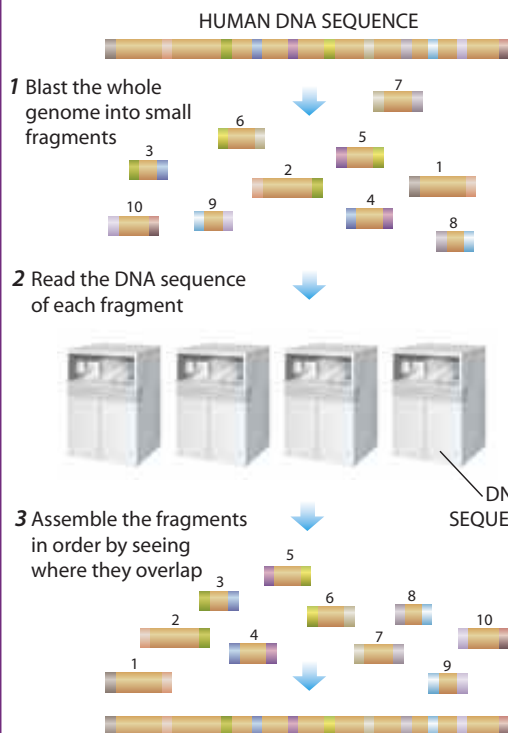
lives," Gilman adds. "So, yes, we'll use our [threefold] coverage to order the public data, and that will give us what we believe to be a very accurate picture of the human genome." In early May the HGP announced it had completed its own working draft as well as a finished sequence for chromosome 21, which is involved in Down's syndrome and many other diseases. (For a full account of the chromosome 21 story, go to www.sciam.com/explorations/2000/051500chrom21 on the World Wide Web.)

Until now, the genome generators have focused on the similarities among us all. Scientists think that 99.9 percent of your genes perfectly match those of the person sitting beside you. But the remaining 0.1 percent of your genes vary—and it is these variations that most interest drug companies. Even a simple single-nucleotide polymorphism (SNP)—a T, say, in one of your gene sequences, where your neighbor has a C—can spell trouble.

The Two Genome-Sequencing Strategies

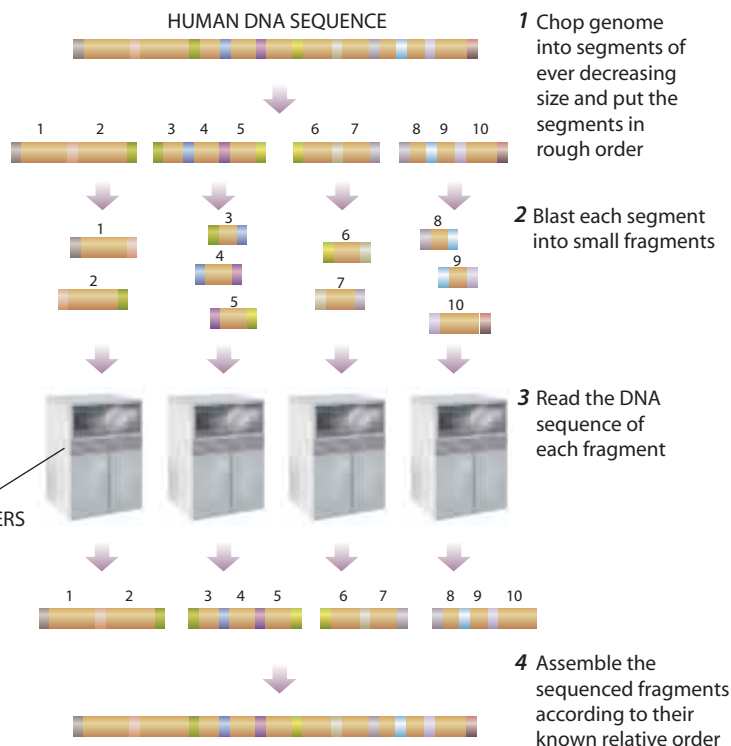
CELERA GENOMICS

WHOLE SHOTGUN APPROACH



HUMAN GENOME PROJECT

NESTED SHOTGUN APPROACH



Because of these tiny genetic variations, Venter claims, many drugs work only on 30 to 50 percent of the human population. In extreme cases, a drug that saves one person may poison another. Venter points to the type II diabetes drug Rezulin, which has been linked to more than 60 deaths from liver toxicity worldwide. "In the future, a simple genetic test may determine whether you're likely to be treated effectively by a given drug or whether you face the risk of being killed by that same drug," Venter predicts. While fleshing out its rough genome, Celera has also been comparing some of the genes with those from other individuals, building up a database of SNPs (pronounced "snips").

Other companies, too, hope to cash in on pharmacogenomics. Drug giants are partnering with smaller genomics-savvy companies to fulfill their gene dreams: Pfizer in New York City has paired with Incyte Genomics in Palo Alto, Calif.; SmithKline Beecham in Philadelphia has

ties to Human Genome Sciences in Rockville; and Eli Lilly in Indianapolis has links to Millennium Pharmaceuticals in Cambridge, Mass. At this point, personalized medicine is still on the lab bench, but some business analysts say it could become an \$800-million market by 2005. As Venter puts it: "This is where we're headed."

But the road is sure to be bumpy. One sticking point is the use of patents. No one blinks when Volvo patents a car design or Microsoft patents a software program, according to John J. Doll, director of the U.S. Patent and Trademark Office's biotechnology division. But many people are offended that biotechnology companies are claiming rights to human DNA—the very stuff that makes us unique. Still, without such patents, a company like Myriad Genetics in Salt Lake City couldn't afford the time and money required to craft tests for mutations in the genes *BRCA1* and *BRCA2*, which have been linked to breast and

ovarian cancer. "You simply must have gene patents," Doll states.

Most scientists agree, although some contend that companies are abusing the public genome data that have been so exactly sequenced—much of them with federal dollars. Dutifully reporting their findings in GenBank, HGP scientists have offered the world an unparalleled glimpse at what makes a human. And Celera's scientists aren't the only ones peering in—in April, GenBank logged roughly 35,000 visitors a day. Some work at companies like Incyte, which mines the public data to help build its own burgeoning catalogue of genes—and patents the potential uses of those genes. Incyte has already won at least 500 patents on full-length genes—more than any other genomics company—and has applied for roughly another 7,000 more. Some researchers complain that such companies are patenting genes they barely understand and, by doing so, restricting future research on

The "Other" Genomes

Comparatively simple organisms are being harnessed to find new drugs for humans

by Julia Karow

What do we have in common with flies, worms, yeast and mice? Not much, it seems at first sight. Yet corporate and academic researchers are using the genomes of these so-called model organisms to study a variety of human diseases, including cancer and diabetes.

The genes of model organisms are so attractive to drug hunters because in many cases the proteins they encode closely resemble those of humans—and model organisms are much easier to keep in the laboratory. "Somewhere between 50 and 80 percent of the time, a random human gene will have a sufficiently similar counterpart in nematode worms or fruit flies, such that you can study the function of that gene," explains Carl D. Johnson, vice president of research at Axys Pharmaceuticals in South San Francisco.

Here's a rundown on the status of the genome projects of the major model organisms today:

The Fruit Fly

The genome sequence for the fruit fly *Drosophila melanogaster* was completed this past March by a collaborative of academic investigators and scientists at Celera Genomics in Rockville, Md.



The researchers found that 60 percent of the 289 known human disease genes have equivalents in flies and that about 7,000 (50 percent) of all fly proteins show similarities to known mammalian proteins.

One of the fly genes with a human counterpart is *p53*, a so-called tumor suppressor gene that when mutated allows cells to become cancerous. The *p53* gene is part of a molecular pathway that causes cells that have suffered irreparable genetic damage to commit suicide. In March a group of scientists, including those at Exelixis in South San Francisco, identified the fly version of *p53* and found that—just as in human cells—fly cells in which the P53 protein is rendered inactive lose the ability to self-destruct after they sustain genetic damage and instead grow uncontrollably. Similarities such as this make flies "a good trade-off" for studying the molecular events that underlie human cancer, according to one of the leaders of the fly genome project, Gerald M. Rubin of the Howard Hughes Medical Institute at the University of California at Berkeley: "You can do very sophisticated genetic manipulations [in flies] that you cannot do in mice because they are too expensive and too big."

The Worm

When researchers deciphered the full genome sequence of the nematode *Caenorhabditis elegans* in 1998, they found that roughly one third of the worm's proteins—more than 6,000—are similar to those of mammals. Now several companies are taking advantage of the tiny size of nematodes—roughly one millimeter—by us-



ing them in automated screening tests to search for new drugs.

To conduct the tests, scientists place between one and 10 of the microscopic worms into the pill-size wells of a plastic microtiter plate the size of a dollar bill. In a version of the test used to screen for diabetes drugs, the researchers use worms that have a mutation in the gene for the insulin receptor that causes them to arrest their growth. By adding various chemicals to the wells, the scientists can determine which ones restore the growth of the worms, an indication that the compounds are bypassing the faulty receptor. Because the cells of many diabetics no longer respond to insulin, such compounds might serve as the basis for new diabetes treatments.

The Yeast

The humble baker's yeast *Saccharomyces cerevisiae* was the first organism with a nucleus to have its genetic secrets read, in 1996.



Approximately 2,300 (38 percent) of all yeast proteins are similar to all known mammalian proteins, which makes yeast a particularly good model organism for studying cancer: scientists first discovered the fundamental mechanisms cells use to control how and when they divide using the tiny fungus.

"We have come to understand a lot about cell division and DNA repair—processes that are important in cancer—from simple systems like yeast," explains Leland H. Hartwell, president and director of the Fred Hutchinson Cancer Research Center in Seattle and co-founder of the Seattle Project, a collaboration between academia and industry. So far Seattle Project scientists have used yeast to elucidate how some of the existing cancer drugs exert their function. One of their findings is that the common chemotherapeutic drug cisplatin is particularly effective in killing cancer cells that have a specific defect in their ability to repair their DNA.

The Mouse

As valuable as the other model organisms are, all new drugs must ultimately be tested in mammals—and that often means mice. Mice are very close to humans in terms of their genome: more than 90 percent of the mouse proteins identified so far show similarities to known human proteins. Ten laboratories across the U.S., called the Mouse Genome Sequencing Network, collectively received \$21 million from the National Institutes of Health last year to lead an effort to sequence the mouse genome. They have completed approximately 3 percent of it, and their goal is to have a rough draft ready by 2003. But that timeline might be sped up: Celera announced in April that it is turning its considerable sequencing power to the task.



JULIA KAROW is an intern at Scientific American.

THE MAJOR PLAYERS

Celera Genomics

A division of PE Corp.

www.celera.com

Stock Symbol: CRA

Headquarters: Rockville, Md.

Lead Executive: J. Craig Venter, president

Major Clients/Partners: Pfizer, Pharmacia, Novartis, Amgen and Takeda Chemical Industries

Strategy: Sell subscriptions to various annotated genomes on-line.

Financing This Year: \$900 million

Key Challenge: Building a business around genome databases.

Competitive Advantages: Extensive DNA-sequencing infrastructure and a large amount of capital.

Human Genome Sciences

www.hgsi.com

Stock Symbol: HGS

Headquarters: Rockville, Md.

Lead Executive: William A. Haseltine, chairman and CEO

Major Clients/Partners: SmithKline Beecham, Takeda Chemical Industries, Schering-Plough, Sanofi-Synthelabo and Merck

Strategies: Develop and market genomics-based drugs; provide drug targets to partners.

Financing This Year: \$525 million

Key Challenge: Bringing genome-based drugs to market.

Competitive Advantages: Patents filed on more than 7,500 human genes; three genomic drugs in human clinical trials.

Incyte Genomics

www.incyte.com

Stock Symbol: INCY

Headquarters: Palo Alto, Calif.

Lead Executive: Roy A. Whitfield, CEO

Major Clients/Partners: 18 of the top 20 pharmaceutical companies

Strategy: Provide nonexclusive commercial access to genomic databases and sell access to DNA clones represented in the databases.

Financing This Year: \$622 million

Key Challenge: Turning genomic information into sustainable business.

Competitive Advantage: A broad data set that includes gene sequences, patterns of gene and protein expression, and genetic variations among individuals.

Millennium Pharmaceuticals

www.mlnm.com

Stock Symbol: MLNM

Headquarters: Cambridge, Mass.

Lead Executive: Mark J. Levin, CEO

Major Clients/Partners: Bayer, Pharmacia, Pfizer and Eli Lilly

Strategies: Develop personalized therapeutics and medical tests; partner with biotech and drug firms in the field of pharmacogenomics.

Financing This Year: \$700 million

Key Challenge: Translating genomic information into proprietary products, including drugs and tests.

Competitive Advantages: Existing alliances with drug developers; recently acquired LeukoSite.

The Human Genome Project

www.nhgri.nih.gov/HGP/

Headquarters: National Human Genome Research Institute (NHGRI), Bethesda, Md.

Joint Collaborators: NHGRI, Department of Energy (DOE) and Wellcome Trust

Lead Executives: Francis S. Collins, NHGRI; Ari Patrinos, DOE; and Michael Morgan, Wellcome Trust

Major Sequencing Centers: Washington University School of Medicine, St. Louis; Baylor College of Medicine, Houston; Sanger Center, Cambridge, England; Whitehead Institute, Cambridge, Mass.; DOE Joint Genome Institute, Walnut Creek, Calif.

Strategy: Map, sequence and annotate the human genome.

Grants Funded This Year: \$112.5 million in 260 grants

Key Challenges: Understanding gene function; encouraging laws to ban genetic discrimination; teaching physicians to use genome information.

Competitive Advantages: Data available within 24 hours of sequencing, at no cost and with no restrictions, via GenBank. Also funding studies of the ethical, legal and social implications of genomics.

those genes. "If data are locked up in a private database and only a privileged few can access it by subscription, that will slow discovery in many diseases," warns Washington University's Wilson.

Incyte president Randal W. Scott, however, sees things differently: "The real purpose of the Human Genome Project is to speed up research discoveries, and our work is a natural culmination of that. Frankly, we're just progressing at a scale that's beyond what most people dreamed of." In March, Incyte launched an e-commerce genomics program—like an amazon.com for genes—that allows researchers to order sequence data or physical copies of more than 100,000 genes on-line. Subscribers to the company's genomics database include drug giants such as Pfizer, Bayer and Eli Lilly. Human Genome Sciences has won more than 100 gene patents—and filed applications for roughly another 7,000—while building its own whopping collection of genes to be tapped by its pharmaceutical partners, which include SmithKline Beecham and Schering-Plough.

The federal government has added confusion to the patent debate. In March, President Bill Clinton and British prime minister Tony Blair released an ambiguous statement lauding open access to raw gene data—a comment some news analysts interpreted as a hit to Celera and other genomics companies that have guarded their genome sequences carefully. Celera and the HGP consortium have sparred over the release of data, chucking early talks of collaboration when the company refused to release its gene sequences immediately and fully into the public domain. The afternoon Clinton and Blair issued their announcement, biotech stocks slid, with some dropping 20 percent by day's end. A handful of genomics companies scrambled to set up press conferences or issue statements that they, indeed, did make available their raw genome data for free. In the following weeks, Clinton administration officials clarified that they still favor patents on "new gene-based health care products."

The sticky part for most patent seekers will be proving the utility of their DNA sequences. At the moment, many patent applications rely on computerized prediction techniques that are often referred to as "in silico biology" [see "The Bioinformatics Gold Rush," on page 58]. Armed with a full or partial gene sequence, scientists enter the data into a

computer program that predicts the amino acid sequence of the resulting protein. By comparing this hypothetical protein with known proteins, the researchers take a guess at what the underlying gene sequence does and how it might be useful in developing a drug, say, or a diagnostic test. That may seem like a wild stab at biology, but it's often enough to win a gene patent. "We accept that as showing substantial utility," Doll says. Even recent revisions to federal gene-patent standards—which have generally raised the bar a bit on claims of usefulness—ask only that researchers take a reasonable guess at what their newfound gene might do.

Testing, Testing

Patents have already led to more than 740 genetic tests that are on the market or being developed, according to the National Institutes of Health. These tests, however, show how far genetics has to go. Several years after the debut of tests for *BRCA1* and *BRCA2*, for instance, scientists are still trying to determine exactly to what degree those genes contribute to a woman's cancer risk. And even the most informative genetic tests leave plenty of questions, suggests Wendy R. Uhlmann, president of the National Society of Genetic Counselors. "In the case of Huntington's, we've got a terrific test," Uhlmann avers. "We know precisely how the gene changes. But we can't tell you the age when your symptoms will start, the severity of your disease, or how it will progress."

Social issues can get in the way, too. After Kelly Westfall's mother tested positive for the Huntington's gene, Westfall, age 30, immediately knew she would take the test as well. "I had made up my mind that if I had Huntington's, I didn't want to have kids," declares Westfall, who lives in Ann Arbor, Mich. But one fear made her hesitate: genetic discrimination. Westfall felt confident enough to approach her boss, who reassured her

that her job was safe. Still, she worried about her insurance. Finally, rather than inform her insurer about the test, Westfall paid for it—some \$450, including counseling—out of pocket. (To her relief, she tested negative.)

The HGP's Collins is among those calling for legislation to protect people like Westfall. A patchwork of federal and state laws are already in place to ban genetic discrimination by insurers or employers, but privacy advocates are lobbying Congress to pass a more comprehensive law. Last February, President Clinton signed an executive order prohibiting all federal employers from hiring, promoting or firing employees on the basis of genetic information. It remains to be seen whether private companies will follow suit.

In the meantime, Celera is now ready to hawk its human genome, complete with crib notes on all the genes, to on-line subscribers worldwide. "It's not owning the data—it's what you do with it," Venter remarks. He envisions a Celera database akin to Bloomberg's financial database or Lexis-Nexis's news archives, only for the genetics set. Which 300 genes are associated with hypertension? What, exactly, does each gene do? These are the kinds of queries Celera's subscribers might pose—for a price. As of press time, Celera planned to offer a free peek at the raw genome data on-line, but tapping into the company's on-line toolkit and full gene notes will cost corporate subscribers an estimated \$5 million to \$15 million a year, according to Gilman. Academic labs will pay a discounted rate: \$2,000 to \$15,000 a year.

Internet surfers can now visit GenBank for free. With all this information available, will scientists really pay Celera? Venter thinks so. "We just have to have better tools," he says. For genomics, that is becoming a familiar refrain. SA

KATHRYN BROWN is a freelance writer based in Alexandria, Va.

Further Information

ARE SEQUENCERS READY TO ANNOTATE THE HUMAN GENOME? E. Pennisi in *Science*, Vol. 287, No. 5461, page 2183; March 24, 2000.

THE HUMAN GENOME PROJECT AND ITS IMPACT ON THE STUDY OF HUMAN DISEASE. E. Green in *Metabolic and Molecular Bases of Inherited Disease*. Edited by Charles R. Scriver. Eighth edition. McGraw-Hill, 2000.

For a primer on genetic testing and a directory of genetic tests, visit GeneTests at www.genetests.org

For more on the ethical, legal and social implications of human genome research, visit the National Human Genome Research Institute's Web site at www.nhgri.nih.gov/ELSI

Plastics.” When a family friend whispered this word to Dustin Hoffman’s character in the 1967 film *The Graduate*, he was advocating not just a novel career choice but an entirely different way of life. If that movie were made today, in the age of the deciphering of the human genome, the magic word might well be “bioinformatics.”

Corporate and government-led scientists have already compiled the three gigabytes of paired A’s, C’s, T’s and G’s that spell out the human genetic code—a quantity of information that could fill

biology—seeks to make sense of it all. In so doing, it is destined to change the face of biomedicine.

“For the next two to three years, the amount of information will be phenomenal, and everyone will be overwhelmed by it,” Myers predicts. “The race and competition will be who can mine it best. There will be such a wealth of riches.”

A whole host of companies are vying for their share of the gold. Jason Reed of the investment banking firm Oscar Gruss & Son in New York City estimates that bioinformatics could be a \$2-billion business within five years. He has compiled information on more than

create extra profits for drug companies by whittling the time it takes to research and develop a drug, thus lengthening the time a drug is on the market before its patent expires.

“Assume I’m a pharmaceutical company and somebody can get [my] drug to the market one year sooner,” explains Stelios Papadopoulos, managing director of health care at the New York investment banking firm SG Cowen. “It could mean you could grab maybe \$500 million in sales you would not have recovered.”

Before any financial windfalls can occur, however, bioinformatics companies must contend with the current plethora

THE

BIOINFORMATICS

GOLD

A \$300-million industry has emerged around turning raw genome data into knowledge for making new drugs

by Ken Howard

more than 2,000 standard computer diskettes. But that is just the initial trickle of the flood of information to be tapped from the human genome. Researchers are generating gigantic databases containing the details of when and in which tissues of the body various genes are turned on, the shapes of the proteins the genes encode, how the proteins interact with one another and the role those interactions play in disease. Add to the mix the data pouring in about the genomes of so-called model organisms such as fruit flies and mice [see “The ‘Other’ Genomes,” on page 53], and you have what Gene Myers, Jr., vice president of informatics research at Celera Genomics in Rockville, Md., calls “a tsunami of information.” The new discipline of bioinformatics—a marriage between computer science and

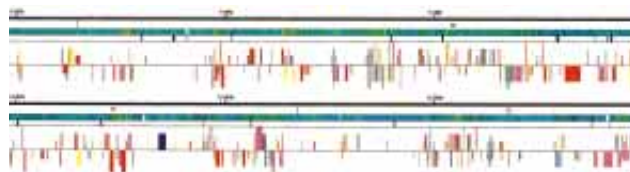
50 private and publicly traded companies that offer bioinformatics products and services. These companies plug into the effort at various points: collecting and storing data, searching databases, and interpreting the data. Most sell access to their information to pharmaceutical and biotechnology companies for a hefty subscription price that can run into the millions of dollars.

The reason drug companies are so willing to line up and pay for such services—or to develop their own expensive resources in-house—is that bioinformatics offers the prospect of finding better drug targets earlier in the drug development process. This efficiency could trim the number of potential therapeutics moving through a company’s clinical testing pipeline, significantly decreasing overall costs. It could also

of genomic data while constantly refining their technology, research approaches and business models. They must also focus on the real challenge and opportunity—finding out how all the shards of information relate to one another and making sense of the big picture.

“Methods have evolved to the point that you can generate lots of information,” comments Michael R. Fannon, vice president and chief information officer of Human Genome Sciences, also in Rockville. “But we don’t know how important that information is.”

Divining that importance is the job of bioinformatics. The field got its start in the early 1980s with a database called GenBank, which was originated by the U.S. Department of Energy to hold the short stretches of DNA sequence that scientists were just beginning to obtain



ATGCGCGTATATGCGA AGGCGCGATATCTCTC
CGTTAACGTAGCAAGA TTATCTTCCGGAGGCG
TCCTGACACAGTATAG CGATACGGAGGCGCG
CGCTAGCTAGCCGCGC ATATCTCTCTGCGCGT
GATCTTAGCTAGCGGG ATATGCGACGTTAACG
CATCATGCTATTGCGA TAGCAAGATCCTGACA
TTCTAGAGGCGGAGGC CAGTATAGCGCTAGCA
GCGATATCTCTCTTAT AGATCCTCACAGTATA
CTTCTTAGCTAGCSGC GCGCTAGCTAGCCGCG
SAGCTAGCCGCATGCA CATCATGCTATTGCGA
GCTAGCGCGACGTTAA TTCTAGAGGCGGCGCG
CGTAGCAAGATCCTCA ATATCTCTCTTATCTTC
CAGTATAGCGCTAGCT TTTGTTCTTSGATAAG
AGCAAGATCCTCACAG ATCCTCACAGTATAGC
TATAGCGCTAGCTAGC GCTAGCGCGCGCTCTC
CGCGCATGCTATTGCG TATGCGACGTTAACGT
ATTCTAGAGGCGGAGG AGCATGCGCGTATATG
CGCGATATCTCTCTTA CATGCGCGTATATGCG
TCTTCTTTGTTCTTST ACGATTCTAGAGGCGCG
CCGGAGGCGCGATATC AGGCGCGATATCTCTC
TCGGAGGCGCGATATC TATTGCGATTCTAGAG
TCTCTTATCTTCTGCG GCGGAGGCGCGATATC
GAGGCGCGATATCTCT TCTCTTATCTTCCGGA
CTTATCTTCTCGATGC GCGCGGATATCTCTCT
GCGTATATGCGACGTT TATCTTCCGGAGGCGCG
AACGTAGCAAGATCCT GATATCTCTCTTATCTT
GACACAGTAAGGCGCT CTCGGAGGCGCGATAT
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TGCTATTGCGATTCTA AGGCGCGATATCTCTC
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ATGCGCGTATATGCGA AGGCGCTTAGCTAGAG
CGTTAACGTAGCAAGA GCGCTTAGCTAGCGGG
TCCTGAATTCTAGAGG CATCATGCTATTGCGA
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RUSH

ATCCTGAGGAGGCGC CGATGCGCGTATATGC
GATATCTCTCTTATCTT GACGTTAACGTAGCAA
CTGCGCGTATATGCGA GATCCTGAGATTCTAG
CGTTAACGTAGCACGG AGGCGGAGGCGCTAT
AGGCGCGATATCTCTC CTTCCGGAGGCGCGAT
TTATCTTCTTAGCTAG ACGGAGGCGCGATATC
CCGCGCGATCTTAGCT TCTCTTAGCTAGCCGC
AGCGGGCATTATCTTC GCGATCTTAGCTAGCG
CGGAGGCGCGATACG GGCATCATGCTATTGCG
GAGGCGCGATATCTCT AGGCGCTTAGCTAGCG
CTTATCTTCTTTGCGA GGCATDGGCTATTGCG
GGCGCGATATCTCTCT ATTCTAGAGGCGGAGG
TATCTTCCGGAGGCGCG CGACGATGCGCGTATA
GATATCTCTCTTATCTT TGGCAGCGTTAACGTAG
CTGACGTTAACGTACG CAAGATCCTGAGCCGC
GAGGCGCGATATCTCT GCGATCTTAGCTAGCG
CTTATCTTCTTAGCTA GGCATCATGCTATTGCG
GCCGCGCGATCTTAGC GATTCTAGAGGCGGAG
TAGCGGGCATCATGCT GCGACGTTAACGTAGC
CGGAGGCGCGATATCT AAGATCCTGACACAGT
CTCTTATCTTCTGATC ATAGCGCTAGCTAAGG
GGCGCGGAGGCGCGA CGCTTAGCTAGCGGGC
TATCTCTCTTATCTTCT ATCATGCTATTGCGAT
AGGCGCGATATCTCTC TCTAGAGGCGGAGGCG
TTATCTTCTCGGAGGCG GACGATGCGCGTATAT
GCGATATCTCTCTTAT GCGACGAGGCGCTTA
CTTCTCGGAGGCGCGA GCTAGCGGGCATCATG
TATCTCTCTCTCTCTCT
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GAGGCGCGGATACGG GCGGAGGCGGACGAT

from a range of organisms. In the early days of GenBank a roomful of technicians sat at keyboards consisting of only the four letters A, C, T and G, tediously entering the DNA-sequence information published in academic journals. As the years went on, new protocols enabled researchers to dial up GenBank and dump in their sequence data directly, and the administration of

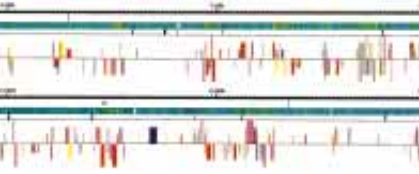
in their plastic cases would take up almost half a mile of shelf space. But GenBank and its corporate cousins are only part of the bioinformatics picture. Other public and private databases contain information on gene expression (when and where genes are turned on), tiny genetic differences among individuals called single-nucleotide polymorphisms (SNPs), the

“The race and competition will be who can mine [the data] best. There will be such a wealth of riches.”

GenBank was transferred to the National Institutes of Health’s National Center for Biotechnology Information (NCBI). After the advent of the World Wide Web, researchers could access the data in GenBank for free from around the globe.

Once the Human Genome Project (HGP) officially got off the ground in 1990, the volume of DNA-sequence data in GenBank began to grow exponentially. With the introduction in the 1990s of high-throughput sequencing—an approach using robotics, automated DNA-sequencing machines and computers—additions to GenBank skyrocketed. GenBank held the sequence data on more than seven billion units of DNA as this issue of *Scientific American* went to press.

Around the time the HGP was taking off, private companies started parallel sequencing projects and established huge proprietary databases of their own. Today companies such as Incyte Genomics in Palo Alto, Calif., can determine the sequence of approximately 20 million DNA base pairs in just one day. And Celera Genomics—the sequencing powerhouse that announced in April that it had completed a rough draft of the human genome [see “The Human Genome Business Today,” on page 50]—says that it has 50 terabytes of data storage. That’s equivalent to roughly 80,000 compact discs, which



structures of various proteins, and maps of how proteins interact [see “Beyond the Human Genome,” on page 64].

Mixing and Matching

One of the most basic operations in bioinformatics involves searching for similarities, or homologies, between a newly sequenced piece of DNA and previously sequenced DNA segments from various organisms. Finding near-matches allows researchers to predict the type of protein the new sequence encodes. This not only yields leads for drug targets early in drug development but also weeds out many targets that would have turned out to be dead ends.

A popular set of software programs for comparing DNA sequences is BLAST (for Basic Local Alignment Search Tool), which first emerged in 1990. BLAST is part of a suite of DNA- and protein-sequence search tools accessible in various customized versions from many database providers or directly through NCBI. NCBI also offers Entrez, a so-called meta-search tool that covers most of NCBI’s databases, including those housing three-

GENETIC DATA are the stuff of bioinformatics, which can be likened to looking for a needle in a haystack. In the fanciful example at the left, the needle is the word “DOG” buried amid a sequence of thousands of A’s, C’s, T’s and G’s, the four units that make up DNA. But bioinformatics also involves comparing genes from various organisms: the other illustrations on this page and on the preceding one are maps of fruit fly chromosomes alongside bar codes showing regions where the fly’s genes are similar to those of others.

THE MAJOR PLAYERS

Lion Bioscience

www.lionbioscience.com

Privately held

Headquarters: Heidelberg, Germany

Lead Executive: Friedrich von Bohlen, CEO

Major Clients/Partners: Bayer, Aventis, Pharmacia

Strategy: Provide enterprise-wide bioinformatics systems and services.

Financing This Year: None

Key Challenges: Continuing to penetrate large to midsize biotechnology and pharmaceutical client base; replicating its success with Bayer.

Competitive Advantage: \$100-million alliance with Bayer creates high visibility and financial leverage.

InforMax

www.informaxinc.com

Privately Held

Headquarters: Bethesda, Md.

Lead Executive: Alex Titomirov, CEO

Major Clients/Partners: Products used by 19 drug companies

Strategy: Provide desktop and enterprise-wide bioinformatics tools.

Financing This Year: None

Key Challenge: Evolving business into enterprise-wide systems.

Competitive Advantage: High market penetration with desktop line of bioinformatics tools.

Oxford Molecular Group

www.oxmol.co.uk

Stock Symbol: OMG (London)

Headquarters: Oxford, England

Lead Executive: N. Douglas Brown, chairman

Major Clients/Partners: Novartis, Glaxo Wellcome, Merck, Pfizer, Smith-Kline Beecham, Abbott Laboratories

Strategy: Provide broad range of drug-discovery research software and services.

Financing This Year: None

Key Challenge: Expanding business into more enterprise-wide products and services.

Competitive Advantage: Owns Genetics Computer Group, whose flagship product, the Wisconsin Package, is considered the industry standard for sequence analysis.

NetGenics

www.netgenics.com

Privately held

Headquarters: Cleveland, Ohio

Lead Executive: Manuel J. Glynias, president and CEO

Major Clients/Partners: Abbott Laboratories, Aventis, IBM

Strategy: Provide enterprise-wide bioinformatics systems and services.

Financing This Year: \$21.3 million

Key Challenge: Continuing to penetrate large and midsize biotechnology and pharmaceutical client base.

Competitive Advantages: Well funded and has relationships with large pharmaceutical companies.

DoubleTwist

www.doubletwist.com

Privately held

Headquarters: Oakland, Calif.

Lead Executive: John Couch, president and CEO

Major Clients/Partners: Derwent Information, Clontech Laboratories, Myriad Genetics, AlphaGene, University of Pennsylvania

Strategy: Provide on-line access to a variety of bioinformatics tools and databases.

Financing This Year: \$37 million

Key Challenges: Providing unique proprietary tools and attracting enough customers to support an Internet-portal business model.

Competitive Advantage: High visibility and potentially large market.

Compugen

www.cgen.com

Privately held

Headquarters: Tel Aviv, Israel

Lead Executive: Mor Amitai, CEO

Major Clients/Partners: Merck, Incyte Genomics, Amgen, Millennium Pharmaceuticals, Bayer, Human Genome Sciences, Janssen Pharmaceutica

Strategies: Produce computer hardware and software to accelerate bioinformatics algorithms; engage in gene discovery and drug development; offer bioinformatics tools via Internet portal.

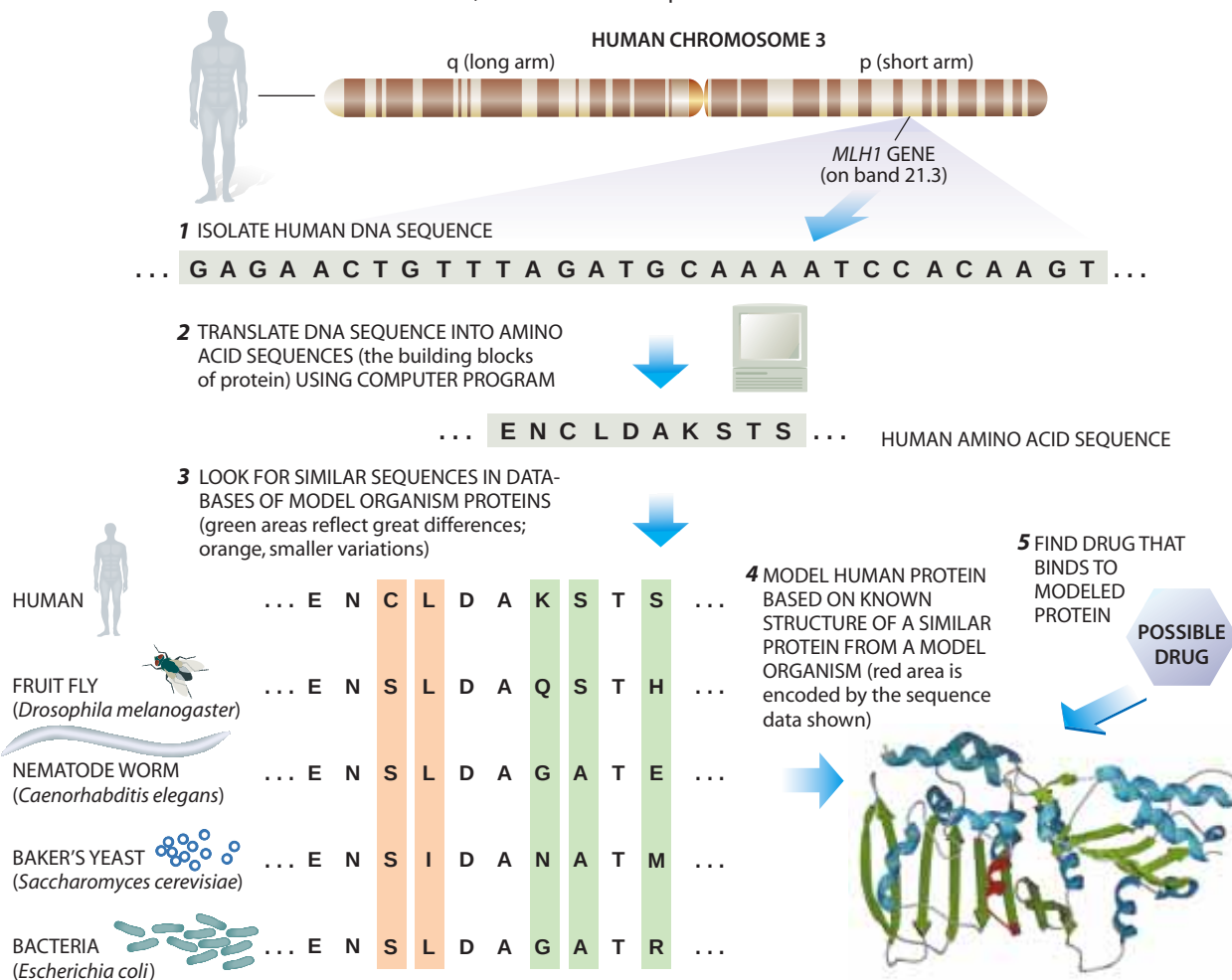
Financing This Year: None

Key Challenges: Evolving business model to drug discovery; expanding product lines; developing Internet-portal business model.

Competitive Advantages: One of the first companies to develop specialized bioinformatics tools, giving it expertise in data mining. Has a stable of proprietary biological data for use in developing drug targets.

Using Bioinformatics to Find Drug Targets

By looking for genes in model organisms that are similar to a given human gene, researchers can learn about the protein the human gene encodes and search for drugs to block it. The *MLH1* gene, which is associated with colon cancer in humans, is used in this example.



dimensional protein structures, the complete genomes of organisms such as yeast, and references to scientific journals that back up the database entries.

An early example of the utility of bioinformatics is cathepsin K, an enzyme that might turn out to be an important target for treating osteoporosis, a crippling disease caused by the breakdown of bone. In 1993 researchers at SmithKline Beecham, based in Philadelphia, asked scientists at Human Genome Sciences to help them analyze some genetic material they had isolated from the osteoclast cells of people with bone tumors. (Osteoclasts are cells that break down bone in the normal course of bone replenishment; they are thought to be overactive in individuals with osteoporosis.)

Human Genome Sciences scientists se-

quenced the sample and conducted database homology searches to look for matches would give them a clue to the proteins that the sample's gene sequences encoded. Once they found near-matches for the sequences, they carried out further analyses and discovered that one sequence in particular was overexpressed by the osteoclast cells and that it matched those of a previously identified class of molecules: cathepsins.

For SmithKline Beecham, that exercise in bioinformatics yielded in just weeks a promising drug target that standard laboratory experiments could not have found without years and a pinch of luck. Company researchers are now trying to find a potential drug that blocks the cathepsin K target. Searches for compounds that bind to and have

the desired effect on drug targets still take place mainly in a biochemist's traditional "wet" lab, where evaluations for activity, toxicity and absorption can take years. But with new bioinformatics tools and growing amounts of data on protein structures and biomolecular pathways, some researchers say, this aspect of drug development will also shift to computers, in what they term "in silico" biology [see "Forget In Vitro—Now It's 'In Silico,'" on next page].

It all adds up to good days ahead for bioinformatics, which many assert holds the real promise of genomics. "Genomics without bioinformatics will not have much of a payoff," states Roland Somogyi, former director of neurobiology at Incyte Genomics who is now at Molecular Mining in Kingstons, Ontario.

Forget In Vitro—Now It's "In Silico"

With the human genome essentially complete, futurists are suggesting that scientists will soon be able to use bioinformatics to model the astronomical number of biochemical reactions that add up to human life. Ken Howard discusses the possibility of such "in silico" biology with complexity expert Stuart A. Kauffman, an external professor at the Santa Fe Institute in New Mexico who is also founder and chief scientific officer of Bios Group in Santa Fe.

Q: What is the promise of bioinformatics and "in silico" biology?

Kauffman: We're entitled to think of the 100,000 genes in a human cell as some kind of parallel-processing chemical computer in which genes are continuously turning one another on and off in some vastly complex network of interaction. Cell-signaling pathways are linked to genetic regulatory pathways in ways we're just beginning to unscramble. The most enormous bioinformatics project in front of us is unscrambling this regulatory network, which controls cell development from the fertilized egg to the adult.

Q: What is the payoff?

Kauffman: We will know which gene to perturb—or which sequences of genes to perturb, and in what order—to guide a cancer cell to nonmalignant behavior or to apoptosis [programmed cell death]. Or to guide the regeneration of some tissue, so that if you happen to have lost half of your pancreas we'll be able to re-

generate your pancreas. Or we'll be able to regenerate the beta cells in people who have diabetes.

Q: What needs to happen to achieve that goal?

Kauffman: It's not going to be merely bioinformatics—there has to be a marriage between new kinds of mathematical tools. Those tools will in general suggest plausible alternative circuits for bits and pieces of the [cell's] regulatory network. And then we're going to have to marry that with new kinds of experiments to work out what the circuitry in cells actually is. And bioinformatics has to be expanded to include experimental design. What we're going to get out of each of these pieces of bioinformatics is hypotheses that need to be tested.

Q: What challenges lie ahead?

Kauffman: Suppose I pick out 10 genes that I know regulate one another, and I try to build a circuit about their behavior. It's a perfectly fine thing, and we should do it. But the downside is the following: those 10 genes have inputs from other genes outside that circuit. So you're taking a little chunk of the circuitry that's embedded in a much larger circuit with thousands of genes in it. You're trying to figure out the behavior of that circuit when you do not know the outside genes it impacted. And that makes that direct approach hard, because you never know what the other inputs are. We've known for years what every neuron is in the lobster gastric ganglia [a nerve bundle going to the animal's digestive

Michael N. Liebman, head of computational biology at Roche Bioscience in Palo Alto, agrees. "Genomics is not the paradigm shift; it's understanding how to use it that is the paradigm shift," he asserts. "In bioinformatics, we're at the beginning of the revolution."

The revolution involves many different players, each with a different strategy. Some bioinformatics companies cater to large users, aiming their products and services at genomics, biotechnology and pharmaceutical companies by creating custom software and offering consulting services. Lion Bioscience, based in Heidelberg, Germany, has been particularly successful at selling "enterprise-wide" bioinformatics tools and services. Its \$100-million agreement with Bayer to build and manage a bioinformatics capability across all of Bayer's divisions was at press time the industry's largest such deal.

Other firms target small or academic users. Web businesses such as Oakland, Calif.-based DoubleTwist and eBioinformatics, which is headquartered in Pleasanton, Calif., offer one-stop Inter-

net shopping. These on-line portals allow users to access various types of databases and use software to manipulate the data.

In May, DoubleTwist scientists announced they had used their technology to determine that the number of genes in the human genome is roughly 105,000, although they said the final count would probably come in at 100,000. For those who would rather have the software behind their own security firewalls, Informax in Rockville, Oxford Molecular Group in England, and others sell shrink-wrapped products.

Making Connections

Large pharmaceutical companies—"big pharma"—have also sought to leverage their genomics efforts with in-house bioinformatics investments. Many have established entire departments to integrate and service computer software and facilitate database access across multiple departments, including new product development, formulation, toxicology and clinical testing. The old

model of drug development often compartmentalized these functions, ghettoizing data that might have been useful to other researchers. Bioinformatics allows researchers across a company to see the same thing while still manipulating the data individually.

In addition to making drug discovery more efficient, in-house bioinformatics can also save drug companies money in software support. Glaxo Wellcome in Research Triangle Park, N.C., is replacing individual packages used by various investigators and departments to access and manipulate databases with a single software platform. Robin M. DeMent, U.S. director of bioinformatics at Glaxo Wellcome, estimates that this will save approximately \$800,000 in staffing support over a three- to five-year period.

To integrate bioinformatics throughout their companies, pharmaceutical giants also forge strategic alliances, enter into licensing agreements and acquire smaller biotechnology companies. Using partners and vendors not only allows big pharma to fill in the gaps in its bioinformatics capabilities but also gives

system], what all the synaptic connections are and what the neurotransmitters are. You have maybe 13 or 20 neurons in the ganglion, and you still can't figure out the behavior of the ganglion. So no mathematician would ever think that understanding a system with 13 variables is going to be an easy thing to do. And [now with the human genome] we want to do it with 100,000 variables. Let me define the state of the network as the current on-and-off values of all 100,000 genes. So how many states are there? Well, there's two possibilities for gene one and two possibilities for gene two and so on, so there's $2^{100,000}$ states, which is roughly $10^{30,000}$. So even if we treat genes as on or off—which is false because they show graded levels of activity—that's $10^{30,000}$ possible states. It is mind-boggling because the number of particles in the known universe is 10^{80} .

Q: Where are we in terms of that problem?

Kauffman: We're at the very beginning, but there's going to be a day when somebody comes in with cancer, and we diagnose it

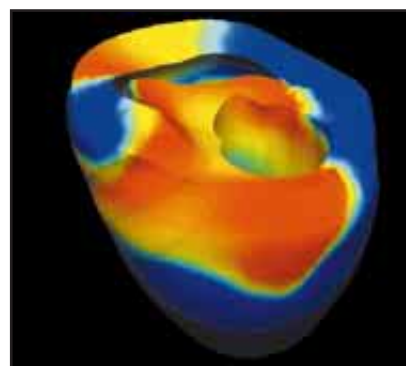
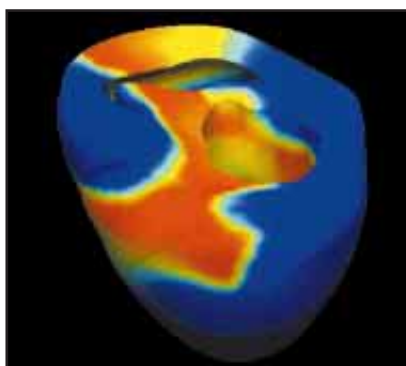
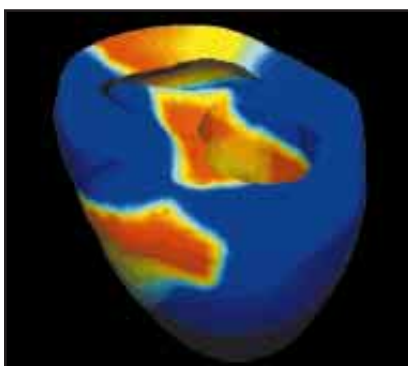
with accuracy not just on the morphology of the cancer cell but by looking at the detailed patterns of gene expression and protein-binding activities in that cell.

Q: How far away is this? One year or 200 years?

Kauffman: The tools will mature within the next 10 to 12 years, and then we'll really start making progress, getting the circuitry for big chunks of the genome and actually understanding how it works. I think 30 to 40 years from now we will have solved major chunks.

For the full transcript of Ken Howard's interview with Stuart A. Kauffman, visit the *Scientific American* Web site at www.sciam.com/interview/2000/060500/kauffman

COMPUTER MODEL OF A HEART in fibrillation shows waves of uncoordinated electrical activity sweeping the organ. The model is based on changes in the expression of four genes whose function is altered during chronic heart failure.



it the mobility to adapt new technologies as they come onto the market rather than constantly overhauling its own systems. "If a pharmaceutical company had a large enough research budget, they could do it all themselves," Somogyi says. "But it's also a question of culture. The field benefits as a whole by providing different businesses with different roles with room to overlap."

Occupying some of that overlap—in resources, products and market capitalization—are companies such as Human Genome Sciences, Celera and Incyte. They straddle the terrain between big pharma and the data integration and mining offered by specialist companies. They have also quickly seized on the degree of automation that bioinformatics has brought to biology.

But with all this variety comes the potential for miscommunication. Getting various databases to talk to one another—what is called interoperability—is becoming more and more key as users flit among them to fulfill their needs. An obvious solution would be annotation—tagging data with names

that are cross-referenced across databases and naming systems. This has worked to a degree. "We've been successful in bringing databases together by annotation: database A to database B, B to C, C to D," explains Liebman of Roche Bioscience. "But annotation in A may change, and by the time you get down to D the references may not have changed, especially with a constant stream of new data." He points out that this problem becomes more acute as the understanding of the biology and the ability to conduct computational analy-

sis becomes more sophisticated. "We're just starting to identify complexities in these queries, and how we store data becomes critical in the types of questions we can ask," he states.

Systematic improvements will help, but progress—and ultimately profit—still relies on the ingenuity of the end user, according to David J. Lipman, director of NCBI. "It's about brainware," he says, "not hardware or software."

KEN HOWARD is a freelance science writer based in New York City.

Further Information

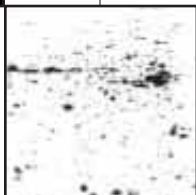
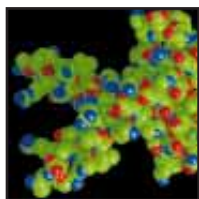
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BioInform, a biweekly newsletter on the subject of bioinformatics, can be accessed at www.bioinform.com

To access the bioinformatics databases maintained by the National Center for Biotechnology Information (NCBI), go to www.ncbi.nlm.nih.gov

BEYOND THE HUMAN GENOME



With all of the DNA that codes for a human in hand, the challenge then becomes what to make of it. Some of the first fruits will come from a new field called proteomics

by Carol Ezzell, *staff writer*

Genes are all the rage right now, but in a sense, at this very moment, they are also becoming passé. Now that all the 100,000 or so genes that make up the human genome have been deciphered, a new industry is emerging to capitalize on when and where those genes are active and on identifying and determining the properties of the proteins the genes encode. The enterprise, which has so far attracted hundreds of millions of dollars in venture capital and other financing, can be lumped under the newly coined term “proteomics.”

“The biggest issue for genomics today is no longer genes,” asserts William A. Haseltine, chairman and chief executive officer of Human Genome Sciences in Rockville, Md. “What’s interesting is what you do with those genes.”

“We have to move on to understand the other elements of the biological process and couple all this [information] together,” agrees Peter Barrett, chief business officer of Celera Genomics, also in Rockville, the company that raced the publicly funded Human Genome Project to sequence the human genome [see “The Human Genome Business Today,” on page 50]. “People took it for granted that the [human] genome would be done this year. Now it’s ‘What do we do next?’”

What’s next, for the most part, are

messenger RNAs (mRNAs) and proteins. If DNA is the set of master blueprints a cell uses to construct proteins, then mRNA is like the copy of part of the blueprint that a contractor takes to the building site every day. DNA remains in the nucleus of a cell; mRNAs transcribed from active genes leave the nucleus to give the orders for making proteins.

Although every cell in the body contains all of the DNA code for making and maintaining a human being, many of those genes are never “turned on,” or copied into mRNA, once embryonic development is complete. Various other genes are turned on or off at different times—or not at all—according to the tissue they are in and their role in the body. A pancreatic beta cell, for instance, is generally full of the mRNA instructions for making insulin, whereas a nerve cell in the brain usually isn’t.

Scientists used to think that one gene equals one mRNA equals one protein, but the reality is much more complicated. They now know that one gene can be read out in portions that are spliced and diced to generate a variety of mRNAs and that subsequent processing of the newly made proteins that those transcripts encode can alter their function. The DNA sequence of the human genome therefore tells only a small fraction of the story about what a specific

cell is doing. Instead researchers must also pay attention to the transcriptome—the body of mRNAs being produced by a cell at any given time—and the proteome, all the proteins being made according to the instructions in those mRNAs.

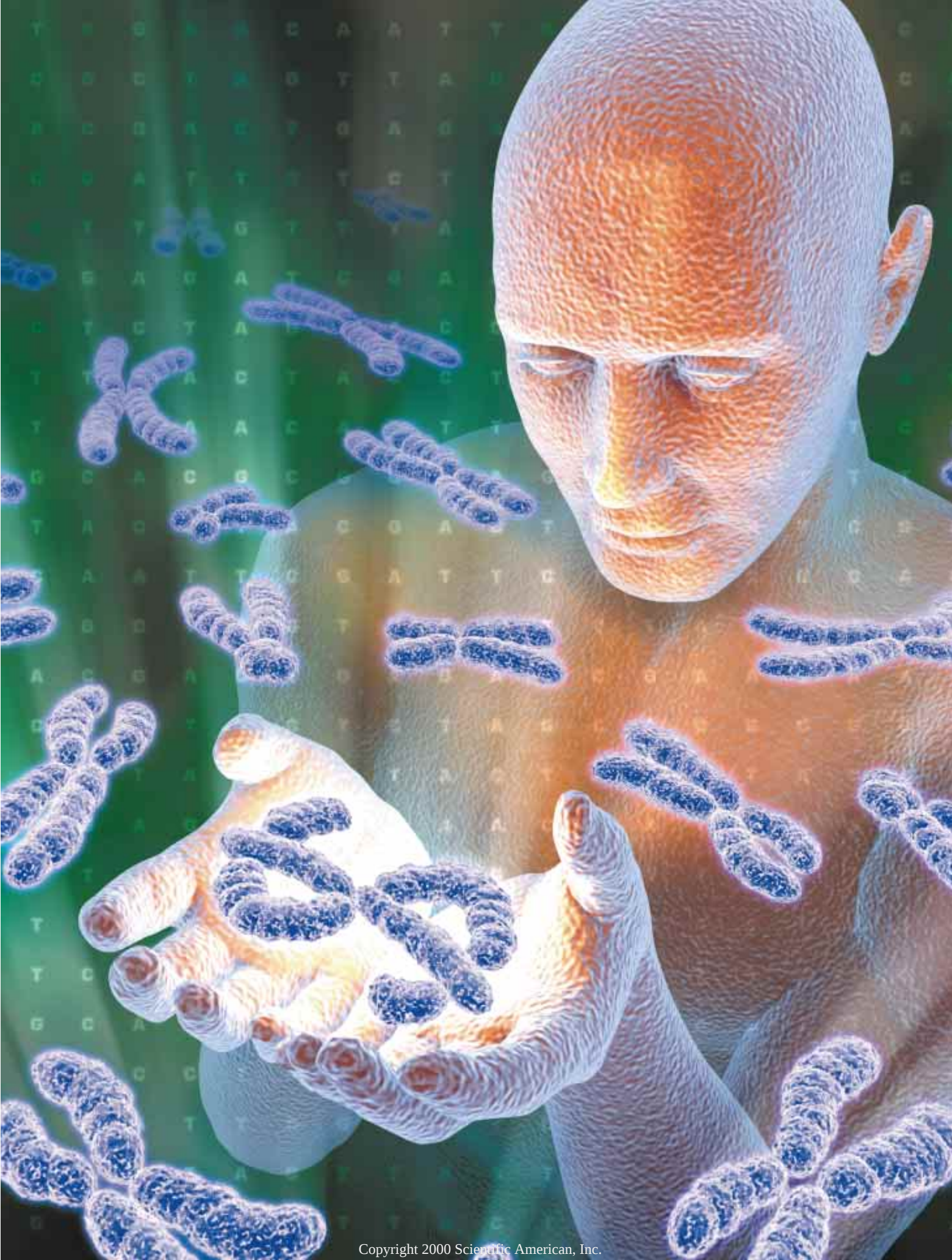
Cashing in on Chips

One of the technologies for studying the human transcriptome is the GeneChip system developed by Affymetrix in Santa Clara, Calif. The system is based on thumbnail-size glass chips called microarrays that are coated with a thin layer of so-called cDNAs, which represent all the mRNAs made by a particular type of cell. (The abbreviation cDNA stands for complementary DNA; it is essentially mRNA artificially translated back into DNA, but without the noncoding sequence gaps, or introns, found in the original genomic DNA.)

To use the system, scientists isolate mRNA from their cellular sample, tag it with a chemical marker and pour it over the chip. By observing where the sample mRNA matches and binds to the cDNA on the chip, they can identify the mRNA sequences in their sample. Earlier this year Affymetrix launched two new sets of chips for analyzing human cell samples. One allows researchers to identify more than 60,000 different human

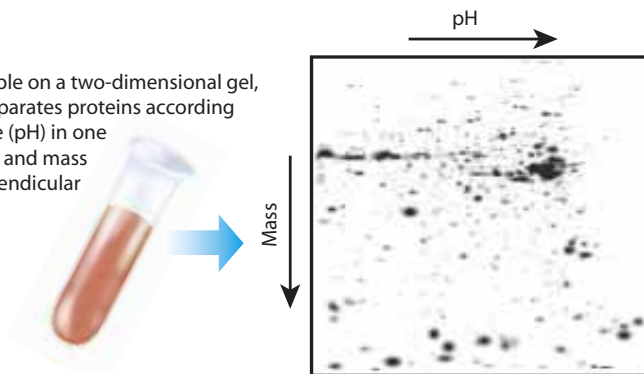
PAYOFF OF GENOMICS will come in the new fields of transcriptomics and proteomics, which concentrate on determining when and where genes are active and on identifying the proteins that those genes encode.

JEFF JOHNSON (opposite page), PAUL HARRISON AND MARK GERSTEIN (this page) (protein structure); JULIO E. CELIS (Danish Center for Human Genome Research, Aarhus) (2-D gel)

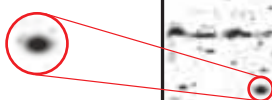


Identifying Unknown Proteins

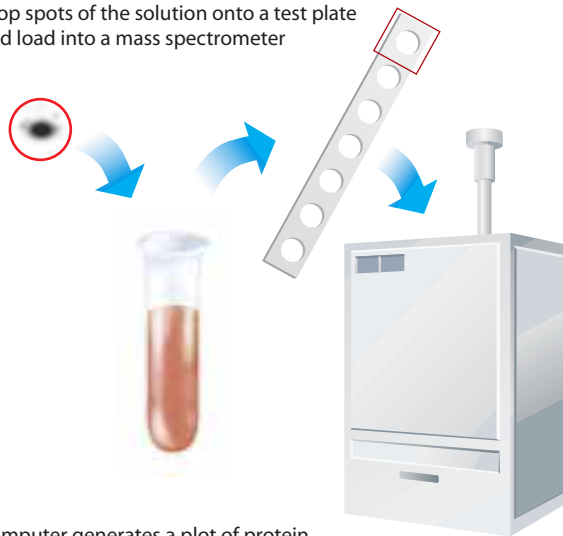
- 1 Run sample on a two-dimensional gel, which separates proteins according to charge (pH) in one direction and mass in a perpendicular direction



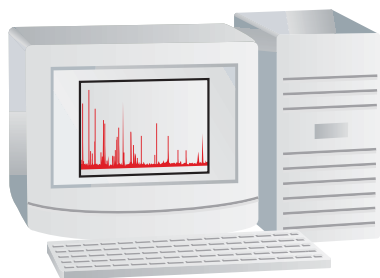
- 2 Cut an unknown protein spot from the gel



- 3 Use enzymes to chop the protein into pieces; drop spots of the solution onto a test plate and load into a mass spectrometer



- 4 Computer generates a plot of protein pieces according to their mass. The plot serves as a fingerprint for identifying the original protein



mRNAs; the other can screen cells for roughly 1,700 human mRNAs related to cancer.

The National Cancer Institute in Bethesda, Md., has been examining the mRNAs produced by various types of cancer cells for more than two years now, in a project called the Human Tumor Gene Index. The index is a partnership between government and academic laboratories as well as a group of drug companies that includes Bristol-Myers Squibb, Genentech, Glaxo Wellcome and Merck. So far they have identified more than 50,000 genes that are active in one or more cancers. For instance, the index has found that 5,692 genes are active in breast cancer cells, including 277 that are not active in other tissues. Compounds that home in on the proteins produced by those 277 genes might serve as good cancer drugs with fewer side effects than current chemotherapies. The National Cancer Institute has also recently begun a multi-million-dollar Tissue Proteomics Initiative in conjunction with the U.S. Food and Drug Administration to identify proteins involved in cancer.

At bottom, mRNA studies are just a means to better understand the proteins in a cell's production line—after all, the proteins are the drug targets. And with researchers expecting that the 100,000 or so human genes will turn out to produce more than a million proteins, that's a lot of targets. Jean-François Formela of Atlas Venture in Boston estimates that within the next decade the pharmaceutical industry will be faced with evaluating up to 10,000 human proteins against which new therapeutics might be directed. That's 25 times the number of drug targets that have been evaluated by all pharmaceutical companies since the dawn of the industry, he says.

Mark J. Levin, CEO of Millennium Pharmaceuticals in Cambridge, Mass., says that large pharmaceutical companies, or "big pharma," need to identify between three and five new drug candidates a year in order to grow 10 to 20 percent a year—the minimum increase shareholders will tolerate. "Right now the major pharma companies are only delivering a half to one-and-a-half entities a year," Levin explains. "Their productivity will not sustain their ability to continue to develop and create shareholder value." Millennium has a relationship with Bayer to deliver 225 pretested "druggable" targets within a few years.

LAURIE GRACE WITH ASSISTANCE FROM THOMAS NEUBERT, New York University AND JOHN VATES, Scripps Research Institute; JULIO E. CELIS, Danish Center for Human Genome Research, Aarhus (gels); PECOPI (mass spectrometer)

"Protein expression is now capturing the imagination of scientists," comments Randall W. Scott, chief scientific officer of Incyte Genomics in Palo Alto, Calif. "It's being able to look not just at a gene and how it's expressed, but at the forms of the protein."

Protein Machines

Scientists at the DNA-sequencing juggernaut Celera are among those getting interested in the study of protein expression, or proteomics. Celera has been in negotiations with GeneBio, a commercial adjunct of the Swiss Institute for Bioinformatics in Geneva, to launch a company dedicated to deducing the entire human proteome. Last year Denis F. Hochstrasser, one of the founders of GeneBio, and his colleagues published plans for a molecular scanner that would automate the now tedious process of separating and identifying the thousands of protein types in a cell.

The current method for studying proteins consists in part of a technique called two-dimensional gel electrophoresis, which separates proteins by

charge and size. In the technique, researchers squirt a solution of cell contents onto a narrow polymer strip that has a gradient of acidity. When the strip is exposed to an electric current, each protein in the mixture settles into a layer according to its charge. Next, the strip is placed along the edge of a flat gel and exposed to electricity again. As the proteins migrate through the gel, they separate according to their molecular weight. What results is a smudgy pattern of dots, each of which contains a different protein.

In academic laboratories, scientists generally use a tool similar to a hole puncher to cut the protein spots from 2-D gels for individual identification by another method, mass spectroscopy [see box on opposite page]. But the companies Large Scale Biology in Vacaville, Calif., and Oxford GlycoSciences (OGS) in Oxford, England, use robots to do it. OGS is under contract with Pfizer to analyze samples of cerebrospinal fluid taken from patients with various stages of Alzheimer's disease.

The machine devised by Hochstrasser and his research group goes one step

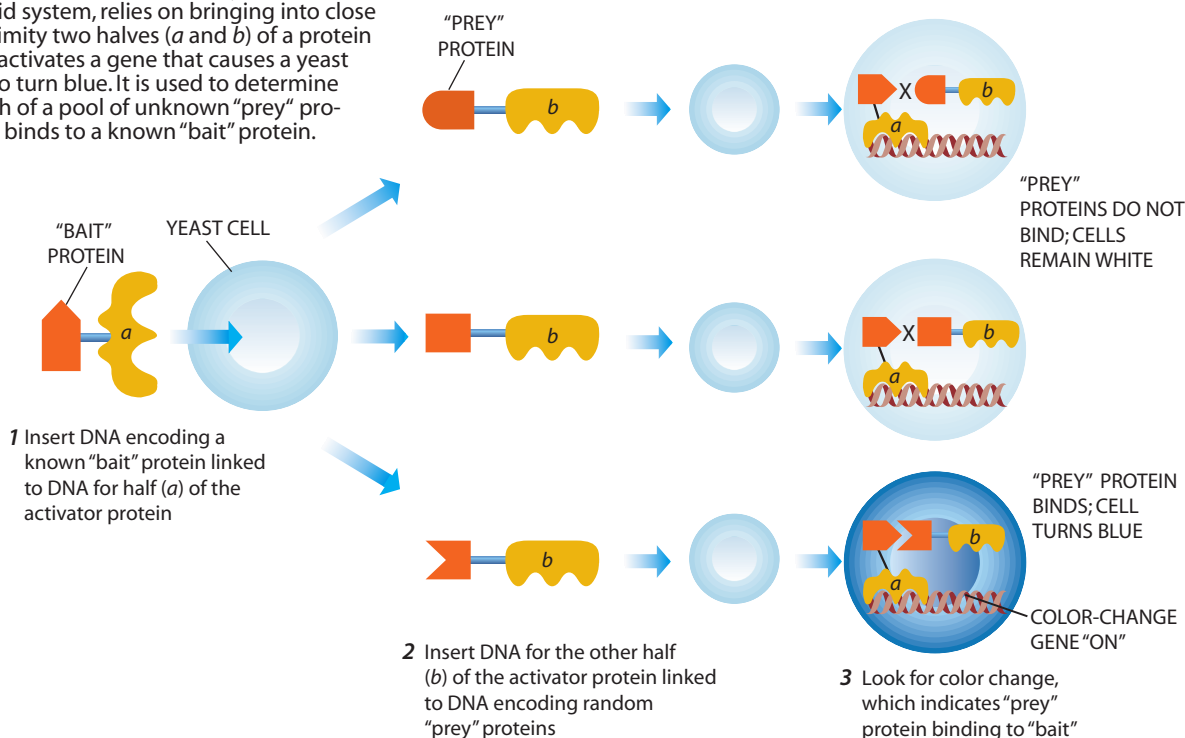
further than the robots used by Large Scale Biology and OGS. It would automatically extract the protein spots from the gels, use enzymes to chop the proteins into bits, feed the pieces into a laser mass spectrometer and transfer the information to a computer for analysis. The instrument manufacturer PE Corporation, which owns Celera, has already agreed to make the machines.

With or without robotic arms, 2-D gels have their problems. Besides being tricky to make, they don't resolve highly charged or low-mass proteins very well. They also do a poor job of resolving proteins with hydrophobic regions, such as those that span the cell membrane. This is a major limitation, because membrane-spanning receptors are important drug targets.

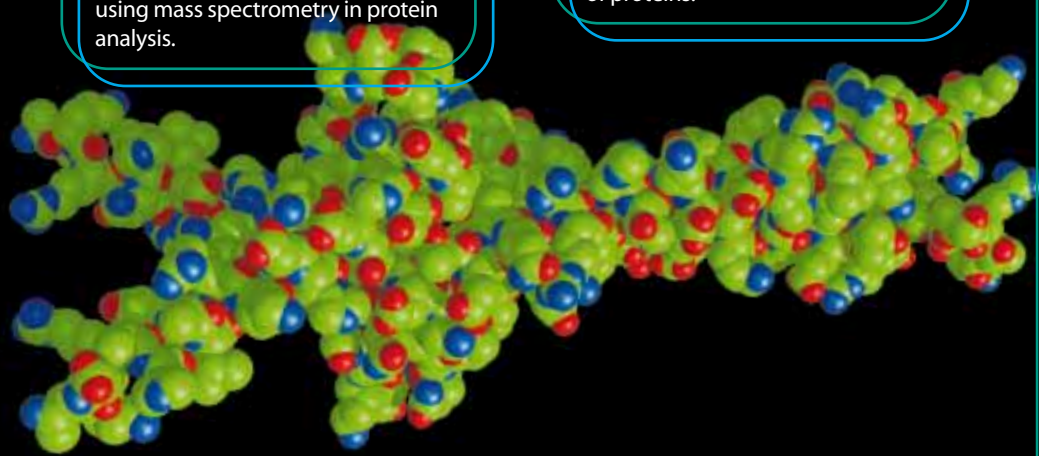
Another method for studying proteomes is what Stephen Oliver of the University of Manchester in England has called "guilt by association": learning about the function of a protein by assessing whether it interacts with another protein whose role in a cell is known. In February researchers at CuraGen in New Haven, Conn.—together

Finding Proteins That Interact

One technique, called the yeast two-hybrid system, relies on bringing into close proximity two halves (*a* and *b*) of a protein that activates a gene that causes a yeast cell to turn blue. It is used to determine which of a pool of unknown "prey" proteins binds to a known "bait" protein.



THE MAJOR PLAYERS



Ciphergen Biosystems

www.ciphergen.com

Plans to go public this year

Headquarters: Palo Alto, Calif.

Lead Executive: William E. Rich, president and CEO

Major Clients/Partners: Human Genome Sciences, Parke-Davis, Aventis, SmithKline Beecham

Strategy: Manufacturing and marketing instruments and chips for protein identification.

Financing This Year: \$28.6 million

Key Challenge: Generating widespread acceptance of mass spectrometry as a common laboratory tool.

Competitive Advantage: A pioneer in using mass spectrometry in protein analysis.

CuraGen

www.curagen.com

Stock Symbol: CRGN

Headquarters: New Haven, Conn.

Lead Executive: Jonathan M. Rothberg, president, chairman and CEO

Major Clients/Partners: Pioneer Hi-Bred International, Genentech, Biogen, Glaxo Wellcome

Strategy: Using proteomics to find new drug targets for the company and its partners.

Financing This Year: \$150 million

Key Challenge: Advancing the company's proteomic technologies while developing its own drugs.

Competitive Advantage: Large capacity for mapping the interactions of proteins.

Hybrigenics

www.hybrigenics.com

Privately Held

Headquarters: Paris

Lead Executive: Donny Strosberg, CEO

Major Clients/Partners: Institut Pasteur, BioSignal, Lynx Therapeutics

Strategies: Providing cell-wide protein interaction maps and drug target discovery and validation services.

Financing This Year: Not disclosed

Key Challenge: Expanding visibility in the U.S.

Competitive Advantage: Delivers thorough analyses with sophisticated bioinformatics.

Large Scale Biology

www.lsb.com

Plans to go public this year

Headquarters: Vacaville, Calif.

Lead Executive: Robert L. Erwin, chairman and CEO

Major Clients/Partners: Glaxo Wellcome, Procter & Gamble, Novartis, Genentech, Dow

Strategy: Providing protein-focused technologies and information to the life sciences industry.

Financing This Year: Not available

Key Challenge: Integrating and promoting business successfully on the heels of its recent merger and initial public offering.

Competitive Advantage: 15 years' experience in proteomics.

Oxford GlycoSciences

www.ogs.com

Stock Symbol: OGS (London)

Headquarters: Oxford, England

Lead Executive: Michael Kranda, CEO

Major Clients/Partners: Pfizer, Bayer, Merck, G.D. Searle, Incyte Genomics

Strategy: Using proteomics and the study of sugar molecules attached to proteins (glycobiology and glycochemistry) to discover new therapeutics and diagnostics.

Financing This Year: £33.2 million (\$49.5 million)

Key Challenge: Seeing clinical validation of its efforts.

Competitive Advantage: Highly automated, large-scale analyses of protein levels.

Myriad Genetics

www.myriad.com

Stock Symbol: MYGN

Headquarters: Salt Lake City

Lead Executive: Peter D. Meldrum, director, president and CEO

Major Clients/Partners: Bayer, Eli Lilly, Pharmacia, Novartis, Roche, Schering and Schering-Plough

Strategies: Selling genetic tests; providing data on protein-protein interactions to help clients find drug targets.

Financing This Year: None

Key Challenge: Running a service business along with developing its own drugs and maintaining its molecular diagnostics business.

Competitive Advantage: Established company that is expanding its business with strong partners.

Affymetrix

www.affymetrix.com

Stock Symbol: AFFX

Headquarters: Santa Clara, Calif.

Lead Executive: Stephen P.A. Fodor, chairman and CEO

Major Clients/Partners: Has installed more than 250 GeneChip systems worldwide

Strategy: Selling gene chips and chip scanners for research and diagnostic use.

Financing This Year: \$150 million

Key Challenge: Finding new markets for its chips and scanners.

Competitive Advantage: The first company to make a business out of gene chips.

with a group led by Stanley Fields of the Howard Hughes Medical Institute at the University of Washington—reported that they had deduced 957 interactions among 1,004 proteins in the baker's yeast *Saccharomyces cerevisiae*. Fields and his colleagues first devised a widely used method for studying protein interactions called the yeast two-hybrid system, which uses known protein “baits” to find “prey” proteins that bind to the “baits” [see box on page 67].

The yeast genome has been known to consist of 6,000 genes since it was sequenced in 1996, but the functions of one third of them have remained mysterious. By figuring out which of the unknown proteins associated with previously identified ones, the CuraGen and University of Washington scientists were able to sort them into functional categories, such as energy generation, DNA repair and aging.

In March, CuraGen announced that it had teamed up with the Berkeley Drosophila Genome Project to produce a protein-interaction map of the fruit fly. “We want to take this massively parallel approach forward,” says Jonathan M. Rothberg, CuraGen's founder, chairman and CEO. The director of the Berkeley project is Gerald M. Rubin, a Howard Hughes Medical Institute researcher at the University of California at Berkeley. He collaborated with Celera on the sequencing of the *Drosophila* genome [see “The ‘Other’ Genomes,” on page 53].

“Yeast was a prototype for us,” Rothberg explains. “But *Drosophila* is good when you want to study an organism with multiple cells.” CuraGen aims to use proteomics to find new drugs for its clients to bring to market. “Our proteomics is 100 percent ‘What does your gene do?’ and ‘Is it a drug target?’” Rothberg states. But CuraGen will also work to identify targets for drugs to sell on its own.

One of CuraGen's competitors is Myriad Genetics, a biotechnology company based in Salt Lake City that is best known for its tests for the *BRCA* genes that contribute to breast and ovarian cancer. Earlier this year Myriad made a deal worth up to \$13 million with Roche to lend its proteomics techniques to finding targets for potential cardiovascular disease drugs.

Myriad also uses a variation of the yeast two-hybrid system but concentrates on specific disease pathways rather than assessing entire genomes. The company has an ongoing alliance

with Schering-Plough, for instance, to plumb the biochemical interactions of proteins encoded by a gene called *MMAC1*, which when mutated can lead to brain and prostate cancer.

Another way to study proteins that has recently become available involves so-called protein chips. Ciphergen Biosystems, a biotechnology company in Palo Alto, is now selling a range of strips for isolating proteins according to various properties, such as whether they

The DNA sequence of the human genome tells only a small fraction of the story about what a specific cell is doing.



dissolve in water or bind to charged metal atoms. The strips can then be placed in Ciphergen's chip reader, which includes a mass spectrometer, for identifying the proteins.

One of the initial uses of Ciphergen's protein chips has been in finding early markers for prostate cancer. Last December, George L. Wright, Jr., of Eastern Virginia Medical School in Norfolk reported using Ciphergen's system to identify 12 candidate “biomarkers” for benign prostatic disease and six such biomarkers for prostate cancer. Tests based on the proteins might be better at discriminating between benign and cancerous prostate conditions than the currently available prostate specific antigen (PSA) assay.

The Structure's the Thing

Identifying all of the proteins in a human is one thing, but to truly understand a protein's function scientists must discern its shape and structure. In an article in *Nature Genetics* last October, a group of well-known structural biolo-

gists led by Stephen K. Burley of the Rockefeller University called for a “structural genomics initiative” to use quasi-automated x-ray crystallography to study normal and abnormal proteins.

Conventional structural biology is based on purifying a molecule, coaxing it to grow into crystals and then bombarding the sample with x-rays. The x-rays bounce off the molecule's atoms, leaving a diffraction pattern that can be interpreted to yield the molecule's over-

all three-dimensional shape. A structural genomics initiative would depend on scaling up and speeding up the current techniques.

The National Institutes of Health is poised to award \$20 million in grants this year for structural genomics to academic centers. And companies are getting into the game, too: Syrrx in La Jolla, Calif., Structural GenomiX in San Diego, and Chalon Biotech in Toronto are founded on developing so-called high-throughput x-ray crystallographic techniques.

Knowing the exact structural form of each of the proteins in the human proteome should, in theory, help drug designers devise chemicals to fit the slots on the proteins that either activate them or prevent them from interacting. Such efforts, which are generally known as rational drug design, have not shown widespread success so far—but then only roughly 1 percent of all human proteins have had their structures determined. After scientists catalogue the human proteome, it will be the proteins—not the genes—that will be all the rage. SA

Further Information

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The Large Hadron



An aerial photograph of the Franco-Swiss border region, showing a mix of green fields and brown patches. A bright yellow line, representing the path of the Large Hadron Collider (LHC) tunnel, curves through the landscape. Three small yellow circles are placed along this line, indicating the locations of caverns for detectors or ancillary equipment. The background shows rolling hills and a clear blue sky.

*The Large Hadron Collider
will be a particle accelerator of
unprecedented energy and complexity,
a global collaboration to uncover
an exotic new layer of reality*

by Chris Llewellyn Smith

Collider

When two protons traveling at 99.999999 percent of the speed of light collide head-on,

the ensuing subatomic explosion provides nature with 14 trillion electron volts (TeV) of energy to play with. This energy, equal to 14,000 times that stored in the mass of a proton at rest, is shared among the smaller particles that make up each proton: quarks and the gluons that bind them together. In most collisions the energy is squandered when the individual quarks and gluons strike only glancing blows, setting off a tangential spray of familiar particles that physicists have long since catalogued and analyzed. On occasion, however, two of the quarks will themselves collide head-on with an energy as high as 2 TeV or more. Physicists are sure that nature has new tricks up her sleeve that must be revealed in those collisions—perhaps an exotic particle known as the Higgs boson, perhaps evidence of a miraculous effect called supersymmetry, or perhaps something unexpected that will turn theoretical particle physics on its head.

The last time that such violent collisions of quarks occurred in large numbers was billions of years ago, during the first picosecond (10^{-12} second) of the big bang. They will start occurring again in about 2005, in a circular tunnel that runs under the Franco-Swiss countryside near Geneva. That's the year that thousands of scientists and engineers from dozens of countries expect to finish building the giant detectors for the Large Hadron Collider (LHC) and start experiments. This vast and technologically challenging project, coordinated by CERN (the European laboratory for particle physics), which will take the major responsibility for constructing the accelerator itself, is already well under way.

The LHC will have about seven times the energy of the Tevatron collider based at Fermi National Accelerator Laboratory in Batavia, Ill., which discovered the long-sought "top" quark in experiments spanning 1992 to 1995 [see "The Discovery of the Top Quark," by Tony M. Liss and Paul L. Tipton; *SCIENTIFIC AMERICAN*, September 1997]. The LHC will achieve its unprecedented energies despite being built within the confines of an existing 27-kilometer tunnel. That tunnel houses CERN's Large Electron-Positron Collider (LEP), which has been used to carry out precision tests of particle physics theory at about 1 percent of the LHC's energy. By using LEP's tunnel, the LHC avoids the problems and vast expense of siting and building a new, larger tunnel and constructing four smaller "injector" accelerators and supporting facilities. But bending the trajectories of the 7-TeV proton beams around the old tunnel's curves will require magnetic fields stronger than those any accelerator has used before. Those fields will be produced by 1,232 15-meter-long magnets installed around 85 percent of the tunnel's circumference. The magnets will be powered by superconducting cables carrying currents of 12,000 amps cooled by superfluid helium to -271 degrees Celsius, two degrees above the absolute zero of temperature.

STRADDLING THE FRANCO-SWISS BORDER, the location of the 27-kilometer tunnel that will house the Large Hadron Collider (LHC) 100 meters below the ground is indicated in gold. Smaller circles mark the positions of caverns that house detectors or ancillary equipment.

To carry out productive physics experiments, one needs more than just high-energy protons. What counts is the energy of collisions between the protons' constituent quarks and gluons, which share a proton's energy in a fluctuating manner. The LHC will collide beams of protons of unprecedented intensity to increase the number of rare collisions between quarks and gluons carrying unusually large fractions of their parent protons' energy. The LHC's intensity, or "luminosity," will be 100-fold greater than that of previous colliders, such as the Tevatron, and 10 times that of the canceled Superconducting Super Collider (SSC). The SSC would have been a direct competitor to the LHC, colliding 20-TeV proton beams in an 87-kilometer-circumference tunnel around Waxahachie, Tex. Relative to the SSC, the LHC's higher intensity will largely compensate for the lower beam energy, but it will make the experiments much harder. Furthermore, such large intensities can provoke problems, such as chaos in the beam orbits, that must be overcome to keep the beams stable and well focused.

At four locations around the LHC's ring, a billion collisions will occur each second, each one producing about 100 secondary particles. Enormous detectors—the largest roughly the height of a six-story building—packed with thousands of sophisticated components will track all this debris. Elaborate computer algorithms will have to sift through this avalanche of data in real time to decide which cases (perhaps 10 to 100 per second) appear worthy of being recorded for full analysis later, "off-line."

Unanswered Questions

As we study nature with higher-energy probes, we are delving into the structure of matter at ever smaller distance scales. Experiments at existing accelerators have explored down to one billionth of one billionth of a meter (10^{-18} meter). The LHC's projectiles will penetrate even deeper into the heart of matter, down to 10^{-19} meter. This alone



SUPERCONDUCTING MAGNET test string is laid out in the assembly hall; 1,232 such magnets will bend the trajectory of the two proton beams to follow the curve of the accelerator's tunnel.

would be enough to whet scientific appetites, but pulses are really set racing by compelling arguments that the answers to major questions must lie in this new domain that the LHC data will illuminate.

In the past 30 years, particle physicists have established a relatively compact picture—the Standard Model—that successfully describes the structure of matter down to 10^{-18} meter. The Standard Model [see box on page 75] succinctly characterizes all the known constituents of matter and three of the four forces that control their behavior. The constituents of matter are six particles called leptons and six called quarks. One of the forces, known as the strong force, acts on quarks, binding them together to form hundreds of particles known as hadrons. The proton and the neutron are hadrons, and a residual effect of the strong force binds them together to form atomic nuclei. The other two forces are electromagnetism and the weak force, which operates only at very short range but is responsible for radioactive beta decay and is essential for the sun's fuel cycle. The Standard

Model elegantly accounts for these two forces as a "unified" electroweak force, which relates their properties despite their appearing very different.

More than 20 physicists have won Nobel Prizes for work that contributed to the Standard Model, from the theory of quantum electrodynamics (the 1965 prize) to the discovery of the neutrino and the tau particle (1995) and the theoretical work of Gerardus 't Hooft and Martinus J. G. Veltman while at the University of Utrecht (1999). Nevertheless, although it is a great scientific achievement, confirmed by a plethora of experiments (some to extraordinary precision), the Standard Model has a number of serious flaws.

First, it does not consistently include Albert Einstein's theory of the properties of space-time and its interaction with matter. This theory, general relativity, provides a beautiful, experimentally very well verified

description of the fourth force, gravity. The difficulty is that the Standard Model is a fully quantum-mechanical theory, whereas general relativity is not quantum-mechanical, and its predictions must therefore break down at very small scales (very far from the domain in which it has been tested). The absence of a quantum-mechanical description of gravity renders the Standard Model logically incomplete.

Second, although it successfully describes a huge range of data with simple underlying equations, the Standard Model contains many apparently arbitrary features. It is too baroque, too byzantine, to be the full story. For example, it does not indicate why there are six quarks and six leptons instead of, say, two or four. Nor does it explain why there are equal numbers of leptons and quarks—is this just a coincidence? On paper, we can construct theories that give better answers and explanations, in which there are deep connections between quarks and leptons, but we do not know which, if any, of these theories is correct.

Third, the Standard Model has an un-

finished, untested element. This is not some minor detail but a central component: a mechanism to generate the observed masses of the particles. Particle masses are profoundly important—altering the mass of the electron, for example, would change all of chemistry, and the masses of neutrinos affect the expansion of the universe. (Neutrinos' masses are at most a few millionths of an electron's mass, but recent experiments indicate they are probably not zero [see "Detecting Massive Neutrinos," by Edward Kearns, Takaaki Kajita and Yoji Totsuka; SCIENTIFIC AMERICAN, August 1999].)

Higgs Mechanism

Physicists believe that particle masses are generated by interactions with a field that permeates the entire universe; the stronger a particle interacts with the field, the more massive it is [see *illustration on page 77*]. The nature of this field, however, remains unknown. It could be a new elementary field, known as the Higgs field after British physicist Peter Higgs. Alternatively, it may be a composite object, made of new particles ("techniquarks") tightly bound together by a new force ("technicolor"). Even if it is an elementary field, there are many variations on the Higgs theme: How many Higgs fields are there, and what are their detailed properties?

Nevertheless, we know with virtually mathematical certainty that *whatever* mechanism is responsible, it must produce new phenomena in the LHC's energy range, such as observable Higgs particles (which would be a manifestation of ripples in the underlying field) or techniparticles. The principal design goal of the LHC is therefore to discover these phenomena and

pin down the nature of the mass-generating mechanism.

The LHC experiments will also be sensitive to other new phenomena that could confirm one or another of the speculative theories that extend or complete the Standard Model. To give just one particularly interesting example, it is widely thought that the more complete theory must incorporate a "super" symmetry. Supersymmetry would greatly increase the web of relations among the elementary particles and forces. Furthermore, so-called local supersymmetry automatically includes gravity, and conversely the only known theory (string theory) that could successfully combine general relativity and quantum mechanics requires supersymmetry. If supersymmetry is correct, physicists have very good reasons to believe that the LHC can find the new particles that it predicts.

These new phenomena may be discovered before the LHC comes into operation. The energy of LEP is still being increased beyond 100 giga-electron volts (GeV) per beam, and in the U.S., Fermilab's Tevatron will start colliding beams of protons and antiprotons again next year after a major upgrade that was completed in 1999. (In the meantime, Fermilab is investigating other physics by firing its protons at fixed targets.) Ei-

ther machine could "scoop" the LHC, but even if they do, they will reveal only the tip of a new iceberg, and the LHC will be where physicists make comprehensive studies of the new processes.

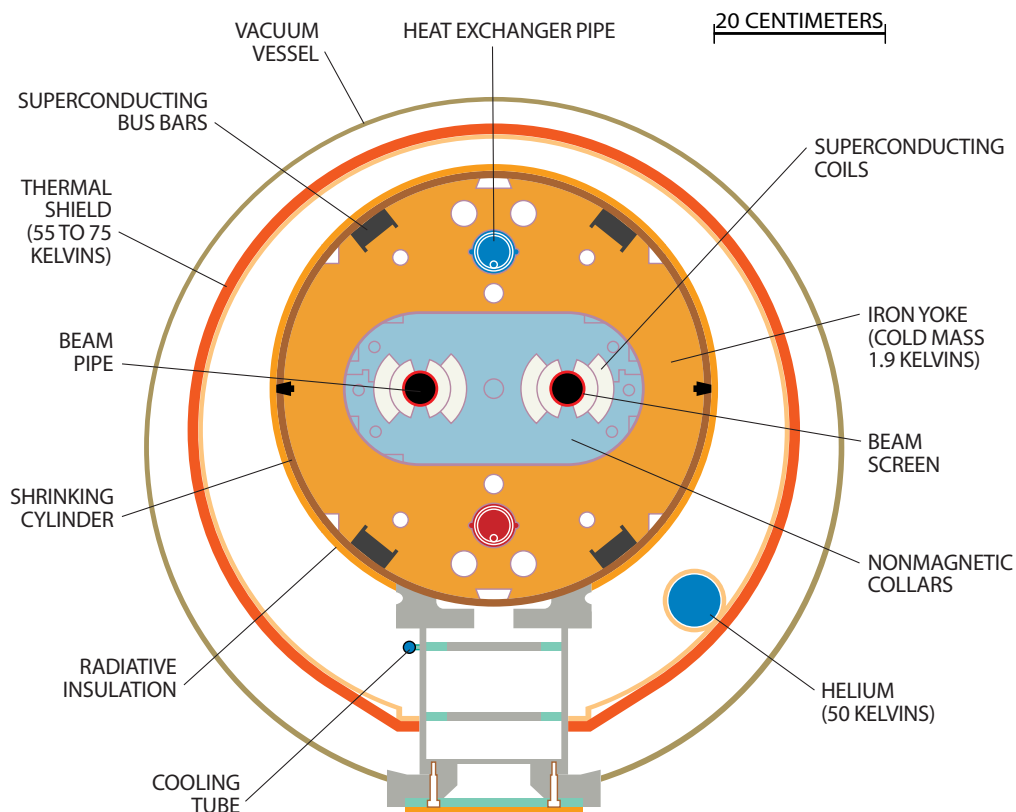
If neither LEP nor the Tevatron observes these new phenomena, then the LHC will pick up the chase. The exploratory range of the LHC overlaps that of today's accelerators, leaving no gaps in which new physics could hide. Moreover, high-precision measurements made in the past seven years at LEP, the Stanford Linear Accelerator Center and Fermilab have essentially eliminated worries that the Higgs boson might be out of reach of the LHC's energy range. It is now clear that either the Higgs boson or other new physics associated with the generation of mass will be found at the LHC.

Emulating the Big Bang

To address this kind of physics requires re-creating conditions that existed just a trillionth of a second after the big bang, a task that will push modern technologies to their limits and beyond. I will discuss just three of the most critical and technologically challenging of the LHC's subsystems: the accelerator magnets, data acquisition and the detectors.

To hold the 7-TeV proton beams on

ACCELERATOR MAGNET is shown in cross section. The superconducting coils carry 12,000 amps of current and must be kept cooled to below two kelvins. Each beam pipe carries one of the two countermoving proton beams. Other magnets focus the beams and bend them to cross at collision points within the detectors.



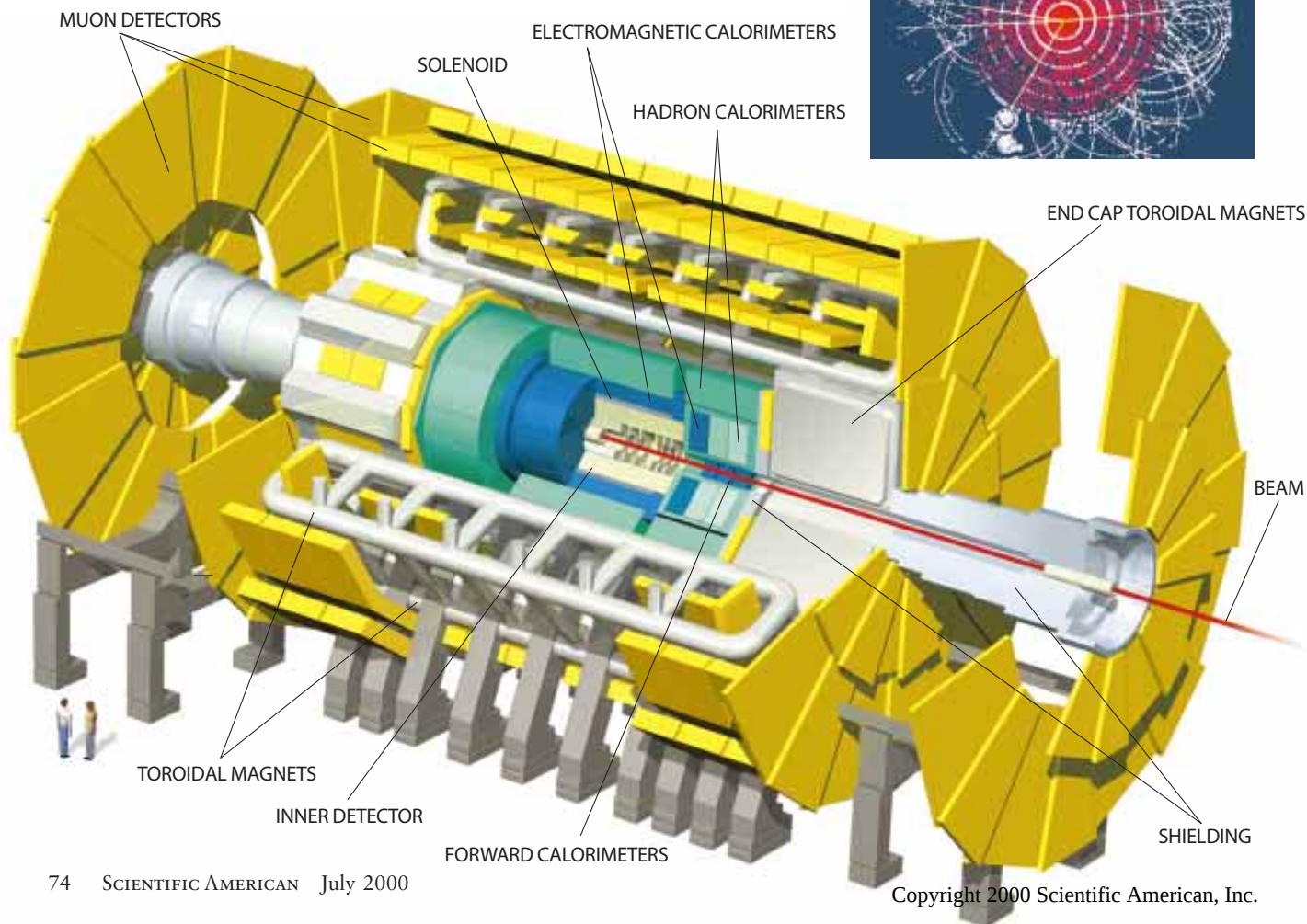
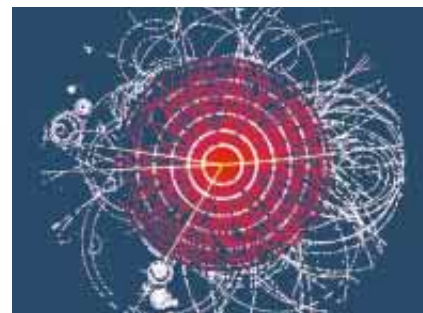
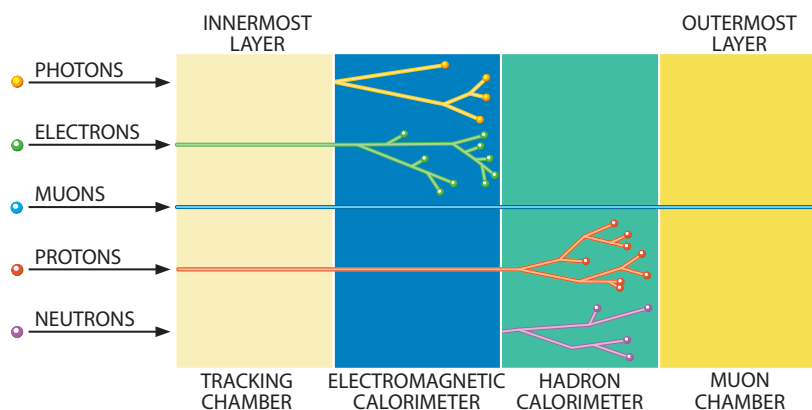
ATLAS DETECTOR (bottom)—A Toroidal LHC Apparatus—uses a novel toroidal magnet system. Protons collide in the center of the detector, producing a spray of particles. The concentric layers of ATLAS detect different species of particles, some precisely tracking the particle trajectories, others (“calorimeters”) measuring the energy carried. The simplified diagram (below, left) illustrates how such layers work. The toroidal magnets curve the tracks of charged particles, allowing their momenta to be measured. The image (below, right) shows simulated data of a collision in which a Higgs particle decays into four muons (yellow tracks).

course, the accelerator bending magnets must sustain a magnetic field of 8.3 tesla, almost 100,000 times the earth’s magnetic field and the highest ever used in an accelerator. They will rely on superconductivity to achieve this: large currents can flow without resistance through thin superconducting wires, resulting in compact magnets that can generate magnetic-field strengths that are unobtainable with conventional magnets made with copper wires [see illustration on preceding page]. To maintain the superconductivity under operating conditions—with 12,000 amps of

current—the magnets’ cores must be held at -271 degrees C around 22.4 kilometers of the tunnel. Cryogenics on this scale has never before been attempted.

In December 1994 a full prototype section of the LHC was operated for 24 hours, demonstrating that the key technical choices for the magnets are correct. Since then, tests on prototypes have simulated about 10 years of running the LHC [see illustration on page 72].

With the 1993 demise of the planned 40-TeV SSC, the 14-TeV LHC is the only accelerator project in the world that can support a diverse research program at the high-energy frontier. The LHC’s strategy of employing beams of the highest possible intensity looked very risky in the early 1990s when the SSC’s design was being finalized, because it was not clear that the detectors would be able to cope with the huge data rates or the radiation damage that would be caused by the vast numbers of particles spraying from the colli-



sions. Thanks to the detector development undertaken for the SSC and the LHC, however, it now seems sound.

The LHC's intense beams present those designing the experiments with remarkable challenges of data acquisition. The beams will consist of proton bunches strung like beads on a chain, 25 billionths of a second apart. At each collision point, pairs of these bunches will sweep through each other 40 million times per second, each time producing about 20 proton-proton collisions. Collisions will happen so often that particles from one collision will still be flying through the detectors when the next one occurs! Of these 800 million collisions per second, only about one in a billion will involve a head-on quark collision. To keep up with this furious pace, information from the detector will go into electronic pipelines that are long enough to hold the data from a few thousand collisions. This will give "downstream" electronics long enough to decide whether a collision is interesting and should be recorded before the data reach the end of the pipeline and are lost. LHC detectors will have tens of millions of readout channels. Matching up all the pipelined signals that originate from the same proton-proton collision will be a mind-boggling task.

When Quarks Collide

Particle detectors are the physicists' electronic eyes, diligently watching each collision for signs of interesting events. LHC will have four particle detectors. Two will be giants, each built like a Russian *matryoshka* doll, with modules fitting snugly inside modules and a beam collision point at the center. Each module, packed with state-of-the-art technology, is custom-built to perform specific observations before the particles fly out to the next layer. These general-purpose detectors, ATLAS and CMS, standing up to 22 meters high, will look for Higgs particles and supersymmetry and will be on the alert for the unexpected, recording as much as possible of the collision debris. Two smaller detectors, ALICE and LHCb, will concentrate on different specific areas of physics.

Both ATLAS and CMS are optimized to detect energetic muons, electrons and photons, whose presence could signal the production of new particles, such as Higgs bosons. Yet they follow very different strategies and use complementa-

The Standard Model

The Standard Model of particle physics encompasses our knowledge of the fundamental particles and how they interact. It contains two kinds of particles—particles of matter and particles that transmit forces. For example, the electromagnetic force between a proton and an electron is generated by photons (particles of light) being passed back and forth between them.

The matter particles come in three families of four, each family differing only by mass. All the matter around us is made of particles from the lightest family. These are "up" quarks, "down" quarks, electrons and electron-neutrinos. The other two families of matter particles exist only ephemerally after being created in high-energy collisions (neutrinos, however, are long-lived).

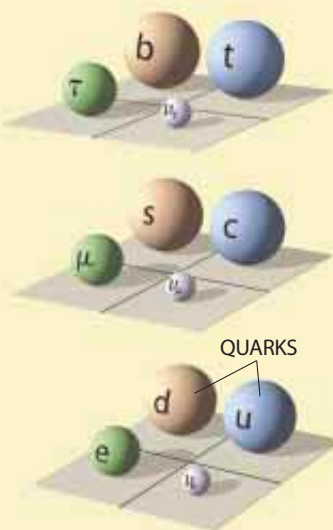
The quarks are stuck together by the strong force, carried by gluons, to form "hadrons," which include the protons and neutrons that combine to make atomic nuclei. Electrons, attracted to these nuclei by the electromagnetic force carried by photons, orbit nuclei to form atoms and molecules. The weak interaction, carried by the W and Z particles, helps to fuel the sun and is responsible when an atomic nucleus decays and emits an electron and a neutrino.

Gravity, the weakest force, is most familiar to us because it acts on mass and we live on a very massive object, the earth. Particles called gravitons are assumed to carry gravity, but they have not been detected, because the force is so weak. Also, gravitons are not yet properly incorporated into the Standard Model.

The entire system of matter and forces (except gravity) is encapsulated in a few simple equations derived from a function (the system's "Lagrangian") that is organized around one core principle (known as local gauge symmetry). Why nature has three families of matter is just one of many questions unanswered by the Standard Model. Considered one of the great intellectual triumphs of 20th-century science, the Standard Model can only be a stepping-stone to a more complete description of nature's forces.

—Graham P. Collins, staff writer

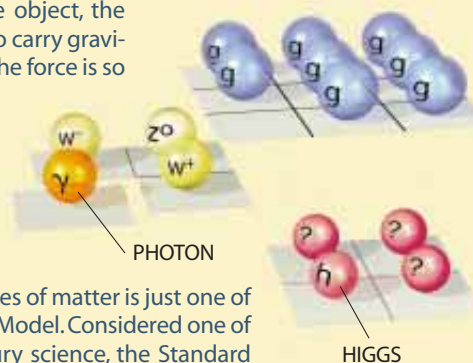
FERMIONS (MATTER)



QUARKS

BOSONS (FORCES)

GLUONS



PHOTON

HIGGS

ry designs and technologies. Years of computer simulations of their performance have shown that they are capable of detecting whatever new phenomena nature may exhibit. ATLAS (A Toroidal LHC Apparatus) is based on an enormous toroidal magnet equipped with detectors designed to identify muons in air [see illustration on opposite page]. CMS (Compact Muon Solenoid) follows the more traditional approach of using chambers inside the return yoke of a very powerful solenoidal magnet to detect muons [see illustration on next page].

Part of the CMS detector will consist of crystals that glow, or scintillate, when electrons and photons enter them. Such crystals are extremely difficult to make, and CMS benefits from the experience gained from the current CERN experiment, L3, which also uses crystals. (The L3 detector is one of four that have

been in operation since 1989 with the LEP collider, which performed precision studies of the weak force that told us that exactly three types of zero- or low-mass neutrino exist.) Before L3, such crystals had been made only in small quantities, but L3 needed 11,000 of them. The type of crystals developed for L3 is now widely used in medical imaging devices. CMS needs over seven times as many crystals made of a more robust material. In due course the superior CMS crystals are likely to have an even bigger effect on the medical field.

ALICE (A Large Ion Collider Experiment) is a more specialized experiment that will come into its own when the LHC collides nuclei of lead with the colossal energy of 1,150 TeV. That energy is expected to "melt" the more than 400 protons and neutrons in the colliding nuclei, releasing their quarks

and gluons to form a globule of quark-gluon plasma (QGP), which dominated the universe about 10 microseconds after the big bang [see “A Little Big Bang,” by Madhusree Mukerjee, *SCIENTIFIC AMERICAN*, March 1999]. ALICE is based around the magnet of the L3 experiment, with new detectors optimized for QGP studies.

There is good evidence that experiments at CERN have already created a

quark-gluon plasma. Over the coming years, Brookhaven National Laboratory’s Relativistic Heavy Ion Collider (RHIC) has a good chance of studying QGP in detail by packing 10 times more energy per nucleon into its collisions than CERN’s present-day program does. The LHC will extend this by a further factor of 30. The higher energy at LHC will complement the more varied range of experiments at RHIC, guaranteeing a thorough study of an important phase in the universe’s early evolution.

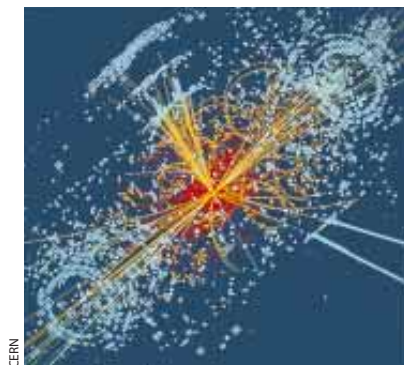
B mesons, the subject of LHCb’s investigations, could help tell us why the universe is made of matter instead of equal amounts of matter and antimatter [see “The Asymmetry between Matter and Antimatter,” by Helen R. Quinn and Michael S. Witherell, *SCIENTIFIC AMERICAN*, October 1998]. Such an imbalance can arise only if heavy quarks and antiquarks decay into their lighter cousins at different rates. The Standard Model can accommodate this phenom-

enon, called CP violation, but probably not enough of it to account completely for the dominance of matter in the universe. Physicists have observed CP violation in the decay of strange quarks, but data on heavy “bottom” quarks and antiquarks, the constituents of B mesons, are needed to establish whether the Standard Model description is correct.

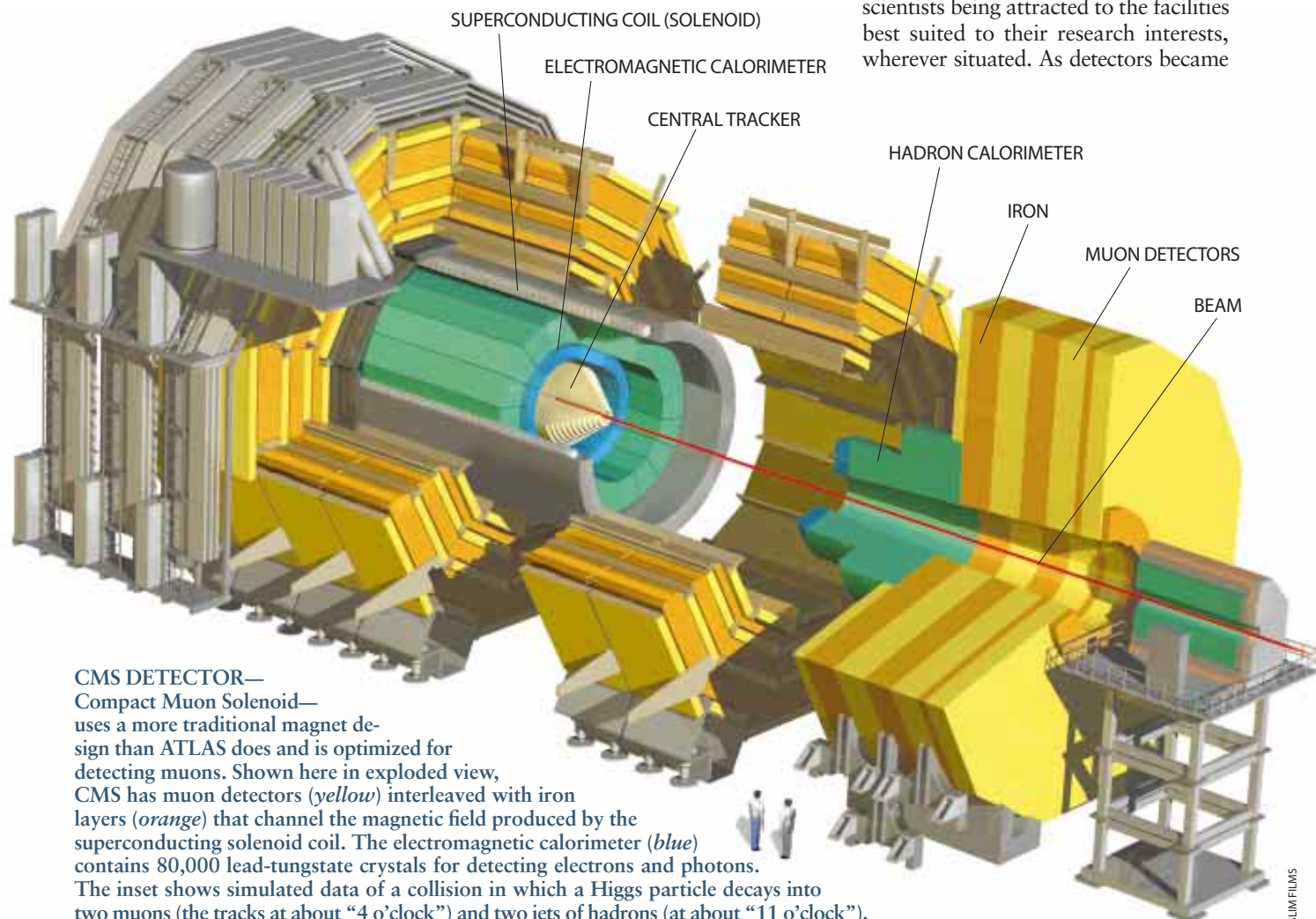
In 1999 experiments began at two “B factories” in California and Japan that can produce tens of millions of B mesons a year. The high luminosity of the LHC beams can churn out a *trillion* B mesons a year for LHCb, allowing much higher precision studies and perhaps uncovering crucial exotic decay modes too rare for the other factories to see clearly.

A Laboratory for the World

Scientific experiments as ambitious as the LHC project are too expensive to be palatable for any one country. Of course, international collaboration has always played a role in particle physics, scientists being attracted to the facilities best suited to their research interests, wherever situated. As detectors became



CERN



CMS DETECTOR—
Compact Muon Solenoid—
uses a more traditional magnet design than ATLAS does and is optimized for detecting muons. Shown here in exploded view, CMS has muon detectors (yellow) interleaved with iron layers (orange) that channel the magnetic field produced by the superconducting solenoid coil. The electromagnetic calorimeter (blue) contains 80,000 lead-tungstate crystals for detecting electrons and photons. The inset shows simulated data of a collision in which a Higgs particle decays into two muons (the tracks at about “4 o’clock”) and two jets of hadrons (at about “11 o’clock”).

SLIM FILMS

How the Higgs Field Generates Mass



"Empty" space, which is filled with the Higgs field, is like a roomful of people chatting quietly.



A particle crossing that region of space is like a celebrity arriving ...



... and attracting a cluster of admirers who impede his progress—he acquires "mass."

larger and costlier, the size and geographic spread of the collaborations that have assisted in their construction have grown correspondingly. (It was the need to facilitate communication between the large LEP collaborations that stimulated the invention of the World Wide Web by Tim Berners-Lee at CERN.)

As originally approved, the LHC accelerator had funding only from CERN's (then) 19 European member states, with construction to occur in two phases on a painfully slow timetable—a poor plan scientifically and more expensive in toto than a faster, single-phase development. Fortunately, additional funds from other countries (which will provide some 40 percent of the LHC's users) will speed up and improve the project. Contributions to the fabrication of accelerator components (in addition to work on the detectors) have been agreed to by Canada, India, Israel, Japan, Russia and the U.S. For example, Japan's KEK laboratory will supply 16 special focusing magnets. The U.S., with more than 550 scientists already involved in the LHC experiments, will furnish the largest national group; accelerator components will be designed and fabricated by Brookhaven, Fermilab and Lawrence Berkeley National Laboratory.

Compared with previous detectors,

ATLAS and CMS will involve at least four times as many participants. Altogether, 5,000 scientists and engineers in more than 300 universities and research institutes in 50 countries on six continents are building the four detectors. When possible, components will be built in the participating institutions, close to students (who get great training by working on such projects) and in collaboration with local industries. The data analysis will also be dispersed. It will be a formidable challenge to manage these high-tech projects, with their stringent technical requirements and tight schedules, while maintaining the democracy and freedom for scientific initiatives that are essential for research to flourish.

Until now, CERN has been primarily a European laboratory. With the LHC, it is set to become a laboratory for the world. Already its 7,000 scientific users amount to more than half the world's experimental particle physicists! In 1994 John Peoples, Jr., then director of Fermilab, summed it up nicely in his 40th-birthday letter to CERN: "For 40 years, CERN has given the world a living demonstration of the power of international cooperation for the advancement of human knowledge. May CERN's next 40 years bring not only new understanding of our Universe, but new levels of understanding among nations." 

How Higgs Particles Are Created



Energy from a particle collision can be like a rumor crossing the room ...



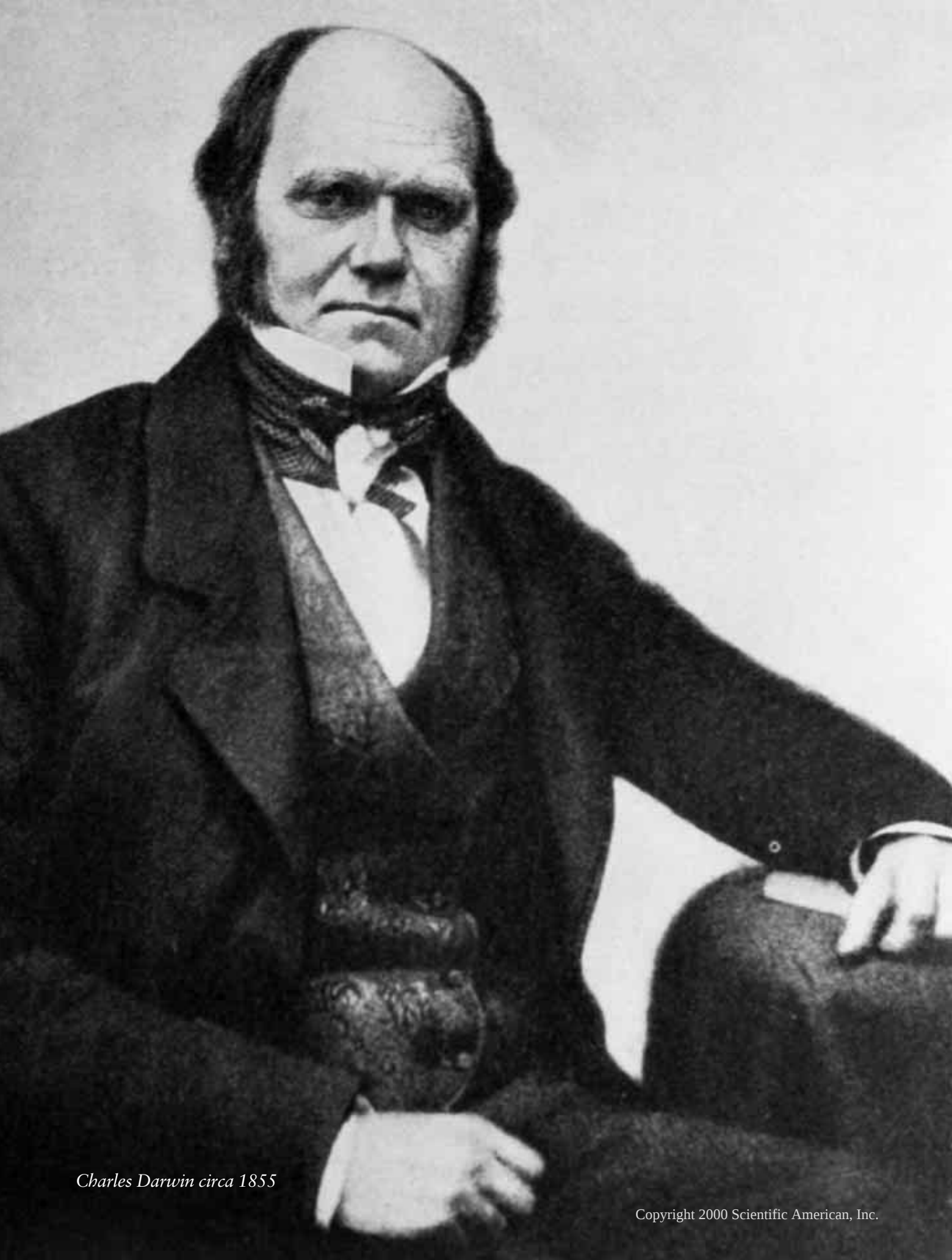
... creating a similar cluster that is self-sustaining, analogous to a Higgs particle itself.

The Author

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Further Information

THE PARTICLE CENTURY. Edited by Gordon Fraser. Institute of Physics, 1998.
SUPERSYMMETRY. Gordon Kane. Perseus Publishing, 2000.
Links to home pages for all four LHC experiments are on the CERN Web site at www.cern.ch/CERN/Experiments.html. Two other excellent sites are <http://pdg.lbl.gov/atlas/atlas.html> and www.particleadventure.org



Charles Darwin circa 1855

Darwin's Influence on Modern Thought

by Ernst Mayr

Clearly, our conception of the world and our place in it is, at the beginning of the 21st century, drastically different from the zeitgeist at the beginning of the 19th century. But no consensus exists as to

Great minds shape the thinking of successive historical periods. Luther and Calvin inspired the Reformation; Locke, Leibniz, Voltaire and Rousseau, the Enlightenment. Modern thought is most dependent on the influence of Charles Darwin

the source of this revolutionary change. Karl Marx is often mentioned; Sigmund Freud has been in and out of favor; Albert Einstein's biographer Abraham Pais made the exuberant claim that Einstein's theories "have profoundly changed the way modern men and women think about the phenomena of inanimate nature." No sooner had Pais said this, though, than he rec-

ognized the exaggeration. "It would actually be better to say 'modern scientists' than 'modern men and women,'" he wrote, because one needs schooling in the physicist's style of thought and

mathematical techniques to appreciate Einstein's contributions in their fullness. Indeed, this limitation is true for all the extraordinary theories of modern physics, which have had little impact on the way the average person apprehends the world.

The situation differs dramatically with regard to concepts in biology. Many biological ideas proposed during the past 150 years stood in stark conflict with what everybody assumed to be true. The acceptance of these ideas required an ideological revolution. And no biologist has been responsible for more—and for more drastic—modifications of the average person's worldview than Charles Darwin.

Darwin's accomplishments were so many and so diverse that it is useful to distinguish three fields to which he made major contributions: evolutionary biology; the philosophy of science; and the modern zeitgeist. Although I will be focusing on this last domain, for the sake of completeness I will put forth a short overview of his contributions—particularly as they inform his later ideas—to the first two areas.

A Secular View of Life

Darwin founded a new branch of life science, evolutionary biology. Four of his contributions to evolutionary biology are especially important, as they held considerable sway beyond that discipline. The first is the nonconstancy of species, or the modern conception of evolution itself. The second is the notion of branching evolution, implying the common descent of all species of living things on earth from a single unique origin. Up until 1859, all evolutionary proposals, such as that of naturalist Jean-Baptiste Lamarck, instead endorsed linear evolution, a teleological march toward greater perfection that had been in vogue since Aristotle's concept of *Scala Naturae*, the chain of being. Darwin further noted that evolution must be gradual, with no major breaks or discontinuities. Finally, he reasoned that the mechanism of evolution was natural selection.

These four insights served as the foundation for Darwin's founding of a new branch of the philosophy of science, a philosophy of biology. Despite the passing of a century before this new branch of philosophy fully developed, its eventual form is based on Darwinian concepts. For example, Darwin introduced historicity into science. Evolutionary biology, in contrast with physics and chemistry, is a historical science—the evolutionist attempts to explain events and processes that have already taken place. Laws and experiments are inappropriate techniques for the explication of such events and processes. Instead one constructs a historical narrative, consisting of a tentative reconstruction of the particular scenario that led to the events one is trying to explain.

For example, three different scenarios have been pro-

posed for the sudden extinction of the dinosaurs at the end of the Cretaceous: a devastating epidemic; a catastrophic change of climate; and the impact of an asteroid, known as the Alvarez theory. The first two narratives were ultimately refuted by evidence incompatible with them. All the known facts, however, fit the Alvarez theory, which is now widely accepted. The testing of historical

narratives implies that the wide gap between science and the humanities that so troubled physicist C. P. Snow is actually nonexistent—by virtue of its methodology and its acceptance of the time factor that makes change possible, evolutionary biology serves as a bridge.

The discovery of natural selection, by Darwin and Alfred Russel Wallace, must itself be counted as an extraordinary philosophical advance. The principle remained unknown throughout the more than 2,000-year history of philosophy ranging from

the Greeks to Hume, Kant and the Victorian era. The concept of natural selection had remarkable power for explaining directional and adaptive changes. Its nature is simplicity itself. It is not a force like the forces described in the laws of physics; its mechanism is simply the elimination of inferior individuals. This process of nonrandom elimination impelled Darwin's contemporary, philosopher Herbert Spencer, to describe evolution with the now familiar term "survival of the fittest." (This description was long ridiculed as circular reasoning: "Who are the fittest? Those who survive." In reality, a careful analysis can usually determine why certain individuals fail to thrive in a given set of conditions.)

The truly outstanding achievement of the principle of natural selection is that it makes unnecessary the invocation of "final causes"—that is, any teleological forces leading to a particular end. In fact, nothing is predetermined. Furthermore, the objective of selection even may change from one generation to the next, as environmental circumstances vary.

A diverse population is a necessity for the proper working of natural selection. (Darwin's success meant that typologists, for whom all members of a class are essentially identical, were left with an untenable viewpoint.) Because of the importance of variation, natural selection should be considered a two-step process: the production of abundant variation is followed by the elimination of inferior individuals. This latter step is directional. By adopting natural selection, Darwin settled the several-thousand-year-old argument among philosophers over chance or necessity. Change on the earth is the result of both, the first step being dominated by randomness, the second by necessity.

Darwin was a holist: for him the object, or target, of selection was primarily the individual as a whole. The geneticists, almost from 1900 on, in a rather reductionist spirit preferred to consider the gene the target of evolu-



*The testing of
historical narratives
bridges science and
the humanities.*

tion. In the past 25 years, however, they have largely returned to the Darwinian view that the individual is the principal target.

For 80 years after 1859, bitter controversy raged as to which of four competing evolutionary theories was valid. "Transmutation" was the establishment of a new species or new type through a single mutation, or saltation. "Orthogenesis" held that intrinsic teleological tendencies led to transformation. Lamarckian evolution relied on the inheritance of acquired characteristics. And now there was Darwin's variational evolution, through natural selection. Darwin's theory clearly emerged as the victor during the evolutionary synthesis of the 1940s, when the new discoveries in genetics were married with taxonomic observations concerning systematics, the classification of organisms by their relationships. Darwinism is now almost unanimously accepted by knowledgeable evolutionists. In addition, it has become the basic component of the new philosophy of biology.

A most important principle of the new biological philosophy, undiscovered for almost a century after the publication of *On the Origin of Species*, is the dual nature of biological processes. These activities are governed both by the universal laws of physics and chemistry and by a genetic program, itself the result of natural selection, which has molded the genotype for millions of generations. The causal factor of the possession of a genetic program is unique to living organisms, and it is totally absent in the inanimate world. Because of the backward state of molecular and genetic knowledge in his time, Darwin was unaware of this vital factor.

Another aspect of the new philosophy of biology concerns the role of laws. Laws give way to concepts in Darwinism. In the physical sciences, as a rule, theories are based on laws; for example, the laws of motion led to the theory of gravitation. In evolutionary biology, however, theories are largely based on concepts such as competition, female choice, selection, succession and dominance. These biological concepts, and the theories based on them, cannot be reduced to the laws and theories of the physical sciences. Darwin himself never stated this idea plainly. My assertion of Darwin's importance to modern thought is the result of an analysis of Darwinian theory over the past century. During this period, a pronounced change in the methodology of biology took place. This transformation was not caused exclusively by Darwin, but it was greatly strengthened by developments in evolutionary biology. Observation, comparison and classification, as well as the testing of competing historical narratives, became the methods of evolutionary biology, outweighing experimentation.

I do not claim that Darwin was single-handedly responsible for all the intellectual developments in this period. Much of it, like the refutation of French mathematician

and physicist Pierre-Simon Laplace's determinism, was "in the air." But Darwin in most cases either had priority or promoted the new views most vigorously.

The Darwinian Zeitgeist

A 21st-century person looks at the world quite differently than a citizen of the Victorian era did. This shift had multiple sources, particularly the incredible advances in technology. But what is not at all appreciated is the great extent to which this shift in thinking indeed resulted from Darwin's ideas.

Remember that in 1850 virtually all leading scientists and philosophers were Christian men. The world they inhabited had been created by God, and as the natural theologians claimed, He had instituted wise laws that brought about the perfect adaptation of all organisms to one another and to their environment. At the same time, the architects of the scientific revolution had constructed a worldview based on physicalism (a reduction to spatiotemporal things or events or their properties), teleology, determinism and other basic principles. Such was the thinking of Western man prior to the 1859 publication of *On the Origin of Species*. The basic principles proposed by Darwin would stand in total conflict with these prevailing ideas.

First, Darwinism rejects all supernatural phenomena and causations. The theory of evolution by natural selection explains the adaptedness and diversity of the world solely materialistically. It no longer requires God as creator or designer (although one is certainly still free to believe in God even if one accepts evolution). Darwin pointed out that creation, as described in the Bible and the origin accounts of other cultures, was contradicted by almost any aspect of the natural world. Every aspect of the "wonderful design" so admired by the natural theologians could be explained by natural selection. (A closer look also reveals that design is often not so wonderful—see "Evolution and the Origins of Disease," by Randolph M. Nesse and George

C. Williams; *SCIENTIFIC AMERICAN*, November 1998.) Eliminating God from science made room for strictly scientific explanations of all natural phenomena; it gave rise to positivism; it produced a powerful intellectual and spiritual revolution, the effects of which have lasted to this day.

Second, Darwinism refutes typology. From the time of the Pythagoreans and Plato, the general concept of the diversity of the world emphasized its invariance and stability. This viewpoint is called typology, or essentialism. The seeming variety, it

was said, consisted of a limited number of natural kinds (essences or types), each one forming a class. The members of each class were thought to be identical, constant, and sharply separated from the members of other essences.

Variation, in contrast, is nonessential and accidental. A triangle illustrates essentialism: all triangles have the same



*The basic principles
of Darwin stood in
total conflict with
prevailing ideas.*

fundamental characteristics and are sharply delimited against quadrangles or any other geometric figures. An intermediate between a triangle and a quadrangle is inconceivable. Typological thinking, therefore, is unable to accommodate variation and gives rise to a misleading conception of human races. For the typologist, Caucasians, Africans, Asians or Inuits are types that conspicuously differ from other human ethnic groups. This mode of thinking leads to racism. (Although the ignorant misapplication of evolutionary theory known as “social Darwinism” often gets blamed for justifications of racism, adherence to the disproved essentialism preceding Darwin in fact can lead to a racist viewpoint.)

Darwin completely rejected typological thinking and introduced instead the entirely different concept now called population thinking. All groupings of living organisms, including humanity, are populations that consist of uniquely different individuals. No two of the six billion humans are the same. Populations vary not by their essences but only by mean statistical differences. By rejecting the constancy of populations, Darwin helped to introduce history into scientific thinking and to promote a distinctly new approach to explanatory interpretation in science.

Third, Darwin’s theory of natural selection made any invocation of teleology unnecessary. From the Greeks onward, there existed a universal belief in the existence of a teleological force in the world that led to ever greater perfection. This “final cause” was one of the causes specified by Aristotle. After Kant, in the *Critique of Judgment*, had unsuccessfully attempted to describe biological phenomena with the help of a physicalist Newtonian explanation, he then invoked teleological forces. Even after 1859, teleological explanations (orthogenesis) continued to be quite popular in evolutionary biology. The acceptance of the *Scala Naturae* and the explanations of natural theology were other manifestations of the popularity of teleology. Darwinism swept such considerations away.

(The designation “teleological” actually applied to various different phenomena. Many seemingly end-directed processes in inorganic nature are the simple consequence of natural laws—a stone falls or a heated piece of metal cools because of laws of physics, not some end-directed process. Processes in living organisms owe their apparent goal-directedness to the operation of an inborn genetic or acquired program. Adapted systems, such as the heart or kidneys, may engage in activities that can be considered goal seeking, but the systems themselves were acquired during evolution and are continuously fine-tuned by natural selection. Finally, there was a belief in cosmic teleology, with a purpose and predetermined goal ascribed to everything in nature. Modern science, however, is unable to substantiate the existence of any such cosmic teleology.)

Fourth, Darwin does away with determinism. Laplace notoriously boasted that a complete knowledge of the cur-

rent world and all its processes would enable him to predict the future to infinity. Darwin, by comparison, accepted the universality of randomness and chance throughout the process of natural selection. (Astronomer and philosopher John Herschel referred to natural selection contemptuously as “the law of the higgledy-piggledy.”) That chance should play an important role in natural processes has been an unpalatable thought for many physicists. Einstein expressed this distaste in his statement, “God does not play dice.” Of course, as previously mentioned, only the first step in natural selection, the production of variation, is a matter of chance. The character of the second step, the actual selection, is to be directional.

Despite the initial resistance by physicists and philosophers, the role of contingency and chance in natural processes is now almost universally acknowledged. Many biologists and philosophers deny the existence of universal laws in biology and suggest that all regularities be stated in probabilistic terms, as nearly all so-called biological laws have exceptions. Philosopher of science Karl Popper’s famous test of falsification therefore cannot be applied in these cases.

Fifth, Darwin developed a new view of humanity and, in turn, a new anthropocentrism. Of all of Darwin’s proposals, the one his contemporaries found most difficult to accept was that the theory of common descent applied to Man. For theologians and philosophers alike, Man was a creature above and apart from other living beings. Aristotle, Descartes and Kant agreed on this sentiment, no matter how else their thinking diverged. But biologists Thomas Huxley and Ernst Haeckel revealed through rigorous comparative anatomical study that humans and living apes clearly had common ancestry, an assessment that has never again been seriously questioned in science. The application of the theory of common descent to Man deprived man of his former unique position.

Ironically, though, these events did not lead to an end to anthropocentrism. The study of man showed that, in spite of his descent, he is indeed unique among all organisms. Human intelligence is unmatched by that of any other creature. Humans are the only animals with true language, including grammar and syntax. Only humanity, as Darwin emphasized, has developed genuine ethical systems. In addition, through high intelligence, language and long parental care, humans are the only creatures to have created a rich culture. And by these means, humanity has attained, for better or worse, an unprecedented dominance over the entire globe.

Sixth, Darwin provided a scientific foundation for ethics. The question is frequently raised—and usually rebuffed—as to whether evolution adequately explains healthy human ethics. Many wonder how, if selection rewards the individual only for behavior that enhances his own survival and reproductive success, such pure selfishness can lead to any sound ethics. The widespread thesis



The common ancestry of humans and apes has never again been seriously questioned.

of social Darwinism, promoted at the end of the 19th century by Spencer, was that evolutionary explanations were at odds with the development of ethics.

We now know, however, that in a social species not only the individual must be considered—an entire social group can be the target of selection. Darwin applied this reasoning to the human species in 1871 in *The Descent of Man*. The survival and prosperity of a social group depends to a large extent on the harmonious cooperation of the members of the group, and this behavior must be based on altruism. Such altruism, by furthering the survival and prosperity of the group, also indirectly benefits the fitness of the group's individuals. The result amounts to selection favoring altruistic behavior.

Kin selection and reciprocal helpfulness in particular will be greatly favored in a social group. Such selection for altruism has been demonstrated in recent years to be widespread among many other social animals. One can then perhaps encapsulate the relation between ethics and evolution by saying that a propensity for altruism and harmonious cooperation in social groups is favored by natural selection. The old thesis of social Darwinism—strict selfishness—was based on an incomplete understanding of animals, particularly social species.

The Influence of New Concepts

Let me now try to summarize my major findings. No educated person any longer questions the validity of the so-called theory of evolution, which we now know to be a simple fact. Likewise, most of Darwin's particular theses have been fully confirmed, such as that of common descent, the gradualism of evolution, and his explanatory theory of natural selection.

I hope I have successfully illustrated the wide reach of Darwin's ideas. Yes, he established a philosophy of biology by introducing the time factor, by demonstrating the importance of chance and contingency, and by showing that theories in evolutionary biology are based on concepts rather than laws. But furthermore—and this is perhaps Darwin's greatest contribution—he developed a set of new principles that influence the thinking of every person: the living world, through evolution, can be explained without recourse to supernaturalism; essentialism or typology is invalid, and we must adopt population thinking, in which all individuals are unique (vital for education and the refutation of racism); natural selection, applied to social groups, is indeed sufficient to account for the origin and maintenance of altruistic ethical systems; cosmic teleology, an intrinsic process leading life automatically to ever greater perfection, is fallacious, with all seemingly teleological phenomena explicable by purely material processes; and determinism is thus repudiated, which places our fate squarely in our own evolved hands.

To borrow Darwin's phrase, there is grandeur in this view of life. New modes of thinking have been, and are being, evolved. Almost every component in modern man's belief system is somehow affected by Darwinian principles. 

This article is based on the September 23, 1999, lecture that Mayr delivered in Stockholm on receiving the Crafoord Prize from the Royal Swedish Academy of Science.



JANE REED/Harvard University

The Author

ERNST MAYR is one of the towering figures in the history of evolutionary biology. Following his graduation from the University of Berlin in 1926, ornithological expeditions to New Guinea fueled his interest in theoretical evolutionary biology. Mayr emigrated to the U.S. in 1931 and in 1953 joined the faculty of Harvard University, where he is now Alexander Agassiz Professor of Zoology, Emeritus. His conception of rapid speciation of isolated populations formed the basis for the well-known neoevolutionary concept of punctuated equilibrium. The author of some of the 20th century's most influential volumes on evolution, Mayr is the recipient of numerous awards, including the National Medal of Science.

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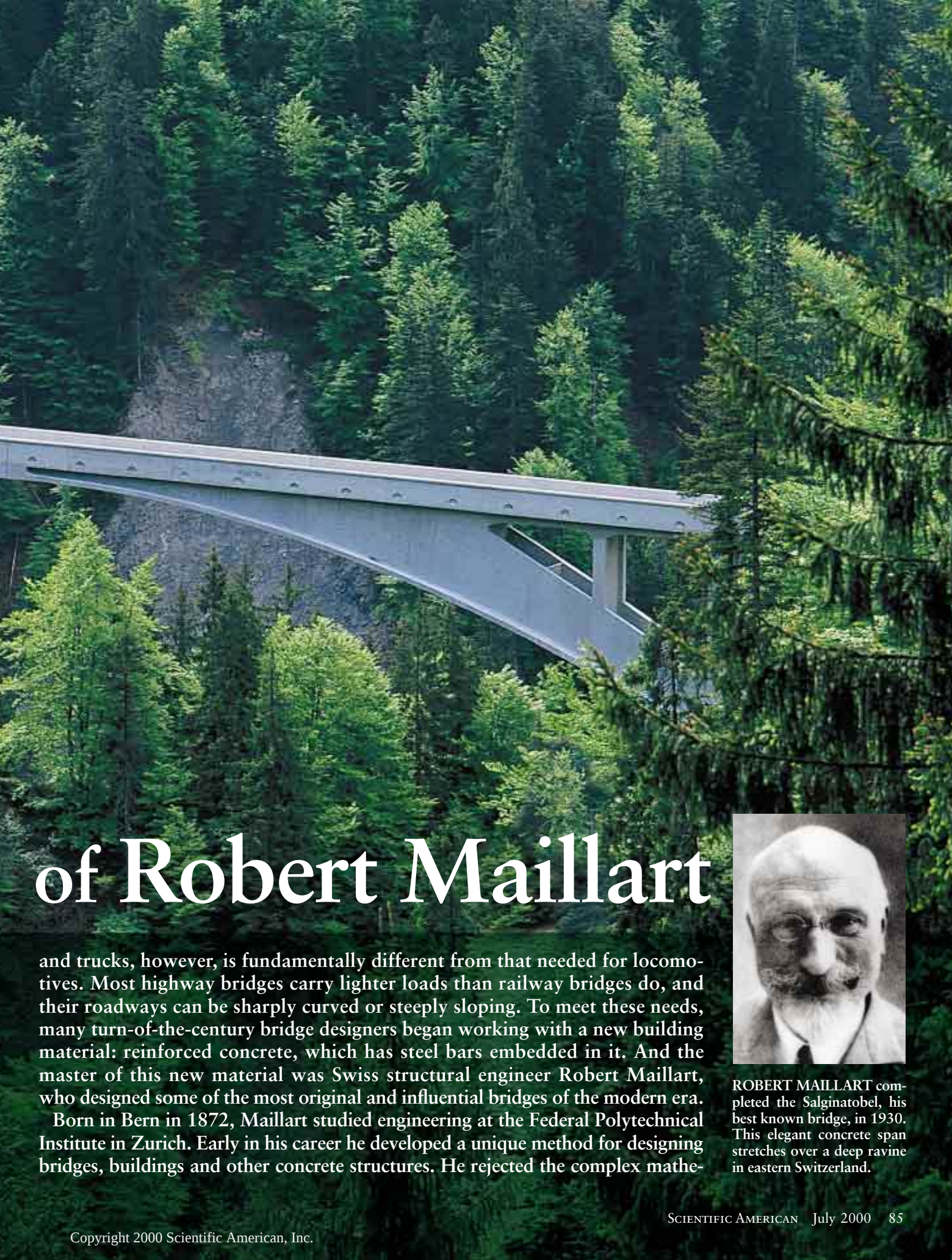
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The Revolutionary Bridges

Swiss engineer Robert Maillart built some of the greatest bridges of the 20th century. His designs elegantly solved a basic engineering problem: how to support enormous weights using a slender arch

by David P. Billington

Just as railway bridges were the great structural symbols of the 19th century, highway bridges became the engineering emblems of the 20th century. The invention of the automobile created an irresistible demand for paved roads and vehicular bridges throughout the developed world. The type of bridge needed for cars



of Robert Maillart

and trucks, however, is fundamentally different from that needed for locomotives. Most highway bridges carry lighter loads than railway bridges do, and their roadways can be sharply curved or steeply sloping. To meet these needs, many turn-of-the-century bridge designers began working with a new building material: reinforced concrete, which has steel bars embedded in it. And the master of this new material was Swiss structural engineer Robert Maillart, who designed some of the most original and influential bridges of the modern era.

Born in Bern in 1872, Maillart studied engineering at the Federal Polytechnical Institute in Zurich. Early in his career he developed a unique method for designing bridges, buildings and other concrete structures. He rejected the complex mathe-



ROBERT MAILLART completed the Salginatobel, his best known bridge, in 1930. This elegant concrete span stretches over a deep ravine in eastern Switzerland.

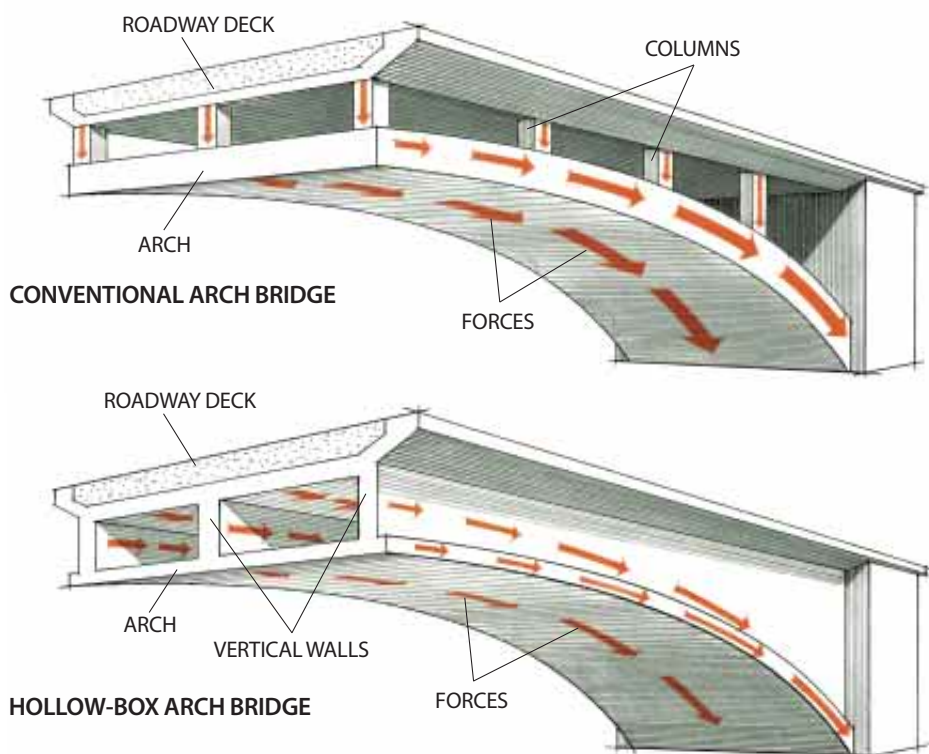


HOLLOW-BOX ARCH was the first important innovation by Maillart in the design of concrete bridges. In a conventional arch bridge (*below, top*), the weight of the roadway is carried by columns to the arch, which must be relatively thick to keep the bending stresses low. But in a hollow-box arch (*below, bottom*), vertical walls connect the roadway deck to the arch, and for most of the bridge's span the load is shared by the deck, walls and arch. In 1901 Maillart used this design to build the slender, inexpensive Zuoz Bridge (*left*).

mathematical analysis of loads and stresses that was being enthusiastically adopted by most of his contemporaries. At the same time, he also eschewed the decorative approach taken by many bridge builders of his time. He resisted imitating architectural styles and adding design elements solely for ornamentation. Maillart's method was a form of creative intuition. He had a knack for conceiving new shapes to solve classic engineering problems. And because he worked in a highly competitive field, one of his goals was economy—he won design and construction contracts because his structures were reasonably priced, often less costly than all of his rivals' proposals. The easiest way to understand his technique is to look closely at the major works that best illustrate his independent vision.

One of the hallmarks of modern engineering is its use of mathematics to analyze designs. Applying the basic principles of mechanics, engineers can calculate the stresses and strains produced in a structure when it is subjected to loads—the weight of vehicles on a bridge, for example, or the force of wind on a skyscraper. Such analysis has enormously increased the ability to predict the performance of those structures, enabling engineers to determine whether their bridges and towers can withstand severe earthquakes or hurricanes. But the dependence on structural analysis has also served, paradoxically, to limit the vision of many designers. All too often, contemporary engineers assume that if a structure cannot be rigorously analyzed, it cannot be built.

Maillart's first important bridge disproved this assumption. In 1900, when Maillart was working for the Zurich construction firm Froté and Wester-



mann, he began the design for a bridge over the Inn River in the small Swiss town of Zuoz. The local officials had initially wanted a steel bridge to span the 30-meter-wide river, but Maillart argued that he could build a more elegant bridge made of reinforced concrete for about the same cost. His plans called for a single-arch bridge with hinges at the abutments and the crown (the bridge's midpoint) to prevent bending stresses at those points. His crucial innovation was incorporating the bridge's arch and roadway into a form called the hollow-box arch, which would substantially reduce the bridge's expense by minimizing the amount of concrete needed.

In a conventional arch bridge the

weight of the roadway is transferred by columns to the arch, which must be relatively thick to keep the bending stresses low under the loads resulting from bridge traffic. In Maillart's design, though, the roadway deck and arch were connected by three vertical walls, forming two hollow boxes running under the roadway [see illustration above]. The big advantage of this design was that for most of the bridge's span the load would be carried by all three parts of the hollow box: the deck, arch and walls. (Near the abutments the load would be funneled into the arch and the abutment hinges.) Because the arch would not have to bear the load alone, it could be much thinner—as little as one third as thick

as the arch in a conventional bridge.

Maillart used a simplified graphical analysis to evaluate the feasibility of his design. A rigorous structural analysis could not be performed, because no engineer at the time could accurately calculate the stresses in a concrete hollow-box arch; the mathematics was simply too complex. When Switzerland's leading authority on structures, Wilhelm Ritter, was called in as a consultant on the Zuoz project, he conceded that he could not mathematically analyze the bridge. Nevertheless, he recognized that Maillart's form was sound and recommended that it be built. The bridge was completed in 1901 and passed a full-scale load test that measured the displacement of the structure when heavy, horse-drawn carts rolled across the span. It was a physical success in spite of being a mathematical mystery.

Over the next two years, however, cracks appeared in the vertical walls near the bridge's abutments. The cracks resulted from the gradual drying of the structure: tension built in the walls as they tried to contract but were restrained by the arch and deck, which were exposed to moisture and thus dried more slowly. This defect did not threaten the bridge's safety, but it motivated Maillart to correct the flaw when he designed his first masterpiece, the 1905 Tavanasa Bridge over the Rhine River in the Swiss Alps.

In this design, Maillart removed the parts of the vertical walls nearest the abutments, which were not essential because they carried no load. In addition to eliminating the cracking problem, the change produced a slender, lighter-looking form [see illustration at right]. This shape perfectly met the bridge's structural requirements: it was shallow at the crown and abutments but deep at the quarter span—the two points halfway between the crown and the abutments—which is precisely where the traffic loads are highest on a three-hinged arch. Sadly, the Tavanasa Bridge was destroyed in a 1927 avalanche that no bridge could have withstood.

Water Tanks and Warehouses

Maillart's innovations went largely unnoticed at first. The Tavanasa Bridge gained little favorable publicity in Switzerland; on the contrary, it aroused strong aesthetic objections from public officials who were more comfortable with old-fashioned stone-faced bridges.

Maillart, who had founded his own construction firm in 1902, was unable to win many more bridge projects, so he shifted his focus to designing buildings, water tanks and other structures made of reinforced concrete.

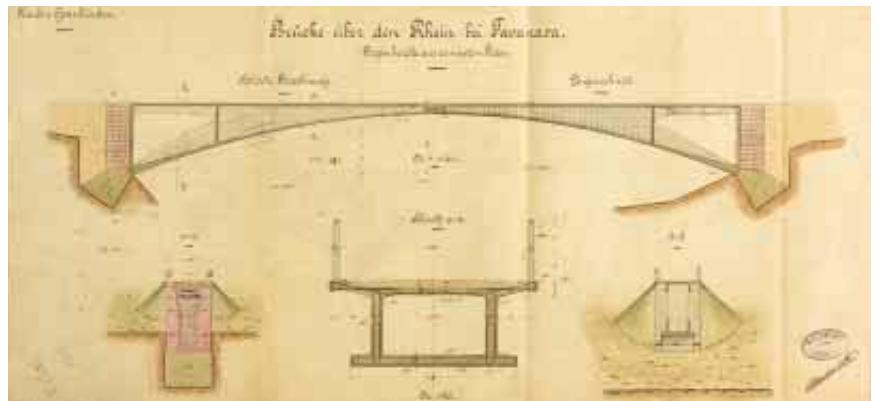
His firm had already built the concrete bases for two large gas tanks in the Swiss city of St. Gallen. These cylindrical structures are filled with water to seal off the gas. Maillart designed the bases to be light, like his bridges—he used only a quarter of the amount of concrete that had been called for in the city's original plans. He made this dramatic reduction by analyzing the structures as if they were ordinary water barrels with vertical staves and circular hoops [see upper illustration on page 91]. In the barrel the water pressure against the staves is balanced by circumferential tension in the hoops, which hold the staves together. Maillart reasoned that the steel bars embedded in the reinforced concrete would perform the same function, so the walls of the base could be relatively thin.

Maillart's graphical analysis of this engineering problem, published in 1907, avoided mathematical complexity, yet it could be applied to any cylindrical wa-

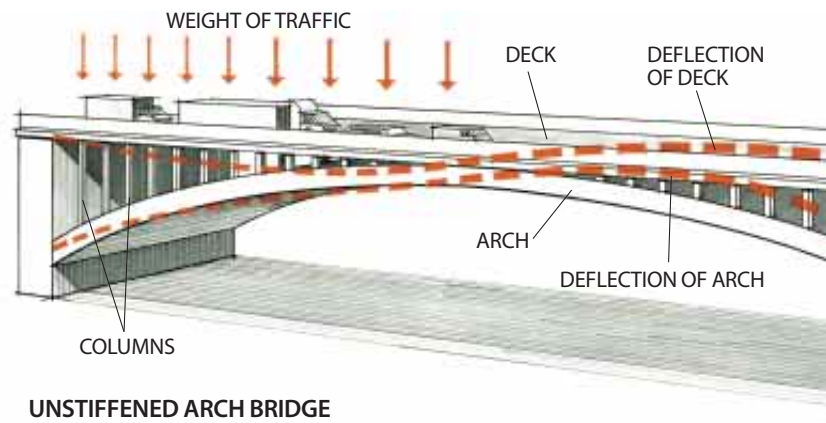
ter container, whatever its specific shape. In the same year, though, a thorough mathematical treatment of the problem appeared, and this approach gradually assumed dominance in the profession. The irony is that the mathematical approach was so complex that engineers could find solutions for only a few simple shapes.

As Maillart began to work on concrete factories, warehouses and other buildings, he confronted another technical problem: how to support the structures' heavily loaded floors. In conventional designs the floors were flat slabs of concrete with horizontal girders running under each slab. The slabs carried the load to the girders, which in turn carried it to the building's columns. Maillart sought a simpler and less costly arrangement in which the concrete slabs

PLANS FOR TAVANASA BRIDGE (top) show Maillart's refinements of his hollow-box arch design. He used only two vertical walls to connect the deck to the arch and removed the sections of the walls nearest the abutments. Completed in 1905 (bottom), this bridge over the Rhine River was destroyed by an avalanche in 1927.



DECK-STIFFENED ARCH was conceived by Maillart as a way to handle live loads—the weight of traffic on a bridge—that are not uniformly distributed. When traffic is resting on only the left side of a conventional arch bridge (*right*), the load will push the left side of the arch downward and the right side upward. (The deflections shown here have been exaggerated.) The arch must be thick enough to keep the bending stresses low. But in a deck-stiffened arch (*far right*), the bridge's deck is made very stiff by adding reinforcing steel to the parapets on both sides of the roadway. The deck is connected by transverse walls to the arch, so it restrains the arch from rising or falling. The design allows for a thin arch because the bending forces on it are minimal.



could be supported without horizontal beams. Other engineers had tried to solve the problem using mathematical analysis, but the results were unsatisfactory. Instead of struggling with formulas, Maillart built models of concrete slabs and conducted load tests on them in his firm's construction yard.

For his first flat-slab building, a 1910 warehouse in Zurich, Maillart employed columns whose tops flare out in capitals that merge with the concrete slab above. These columns provided more support by substantially reducing the free span of the slab. But they also served an aesthetic purpose: Maillart designed the capitals so that they flowed in a smooth hyperbolic curve from the horizontal slab to the vertical octagonal columns.

He used similar columns for the Filter Building in Rorschach, Switzerland, constructed in 1912 [see *lower illustration on page 91*]. These designs illustrate Maillart's search for forms that were beautiful, functional and inexpensive.

A Voice in the Wilderness

Starting in 1912, Maillart's firm prospered by taking on large projects in Czarist Russia, which was just beginning to industrialize. But the outbreak of World War I trapped Maillart and his family in Russia, and he lost his fortune and nearly his life during the Communist revolution. He returned to Switzerland in 1919 and a few years later began to work on concrete bridges again. His

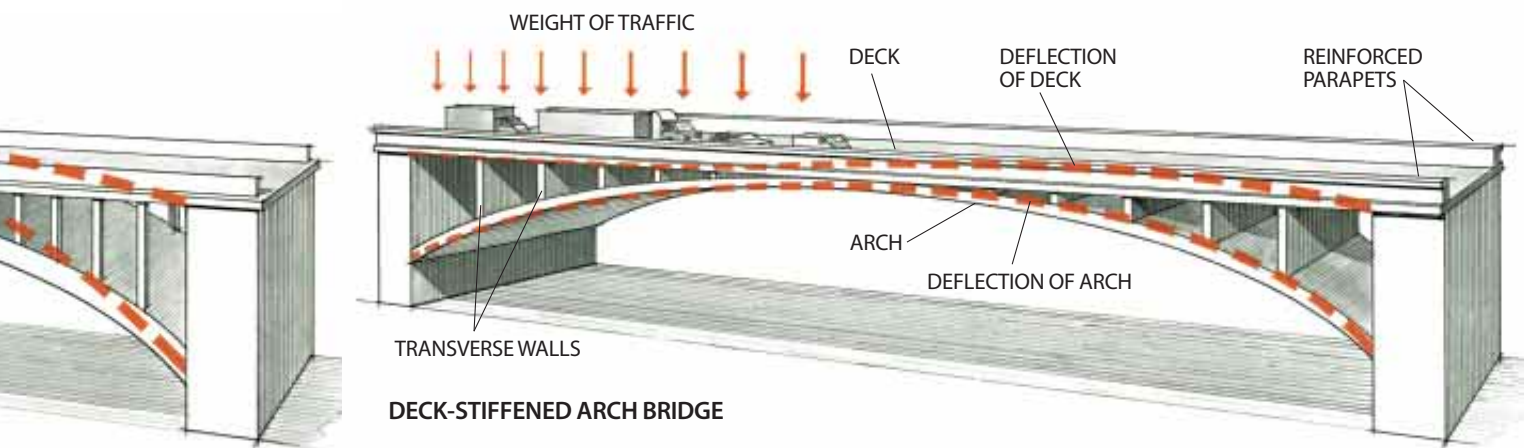
most important breakthrough during this period was the development of the deck-stiffened arch, the first example of which was the Flienglibach Bridge, built in 1923. The idea sprang from Maillart's analysis of the effect of live loads (that is, the weight of the traffic on a bridge) when they are added to a dead load (the weight of the bridge itself).

An arch bridge is somewhat like an inverted cable. A cable curves downward when a weight is hung from it, and the tension in the cable balances the weight. An arch bridge curves upward to support the roadway, and the compression in the arch balances the dead load. But once the engineer has fixed the arch's form to fit the dead load, it cannot be changed. The addition of



EVOLUTION OF DESIGN by Maillart is seen by comparing the 1925 Valtschielbach Bridge (*above*) with the 1933 Schwandbach Bridge (*right and opposite page*). The Valtschielbach, located near the town of Donath in southeastern Switzerland, has Romanesque stone abutments, a smoothly curved arch and a straight roadway deck. The Schwandbach, set in the forests south of Bern, has no stone abutments, its arch is polygonal, and its roadway is horizontally curved.





live loads will cause the arch to bend, especially when the loads are asymmetric—for example, when a heavy truck is resting on one side of the bridge's span. The arch must be strong and thick enough to resist the bending.

For aesthetic reasons, however, Maillart wanted a thinner arch. His solution was to connect the arch to the roadway deck with transverse walls [see *illustration above*]. Because the arch and deck must then bend together, the forces that cause bending (what engineers call the bending moment) would be distributed between the arch and deck in proportion to their relative stiffness. If the deck is much stiffer than the arch, Maillart reasoned, the bending moment would be almost completely on the deck and

the effect on the arch would be negligible. In this way, Maillart justified making the arch as thin as he could reasonably build it. He was able to stiffen the deck of the Flienglibach Bridge by adding more reinforcing steel to the parapets on both sides of the roadway, which also served as guardrails for the bridge traffic.

Maillart's analysis accurately predicted the behavior of the bridge, as shown in full-scale load tests. But the leading authorities of Swiss engineering—the professors at the Federal Polytechnical Institute, Maillart's alma mater—would argue against his methods for the next quarter of a century. Maillart's academic foes saw his approach as frivolous and dangerous. They insisted on the ne-

cessity of a thorough mathematical treatment requiring detailed study of the interaction of the deck, walls and arch. This approach, though, is often difficult to apply in the real world, because it leads to a huge number of simultaneous equations, even for a small bridge. Today such problems can be readily solved by computer, but the mathematical focus can lead engineers away from thinking creatively about bridge design.

Over the next 10 years, Maillart concentrated on refining the visual appearance of the deck-stiffened arch. We can see this improvement by comparing his 1925 Valterschielbach Bridge to his 1933 Schwandbach Bridge. Both arches are extraordinarily thin, but the earlier bridge is more conventional—it has Romanesque

BARRY ROSS (illustration)





MAILLART'S LATER BRIDGES illustrate his continual quest for new forms. The 1936 Vessy Bridge (above, right) on the outskirts of Geneva has a broken arch—its underside comes to a point at the bridge's crown. The X-shaped cross walls supporting the bridge's roadway deck (above, left) feature horizontal lines produced by the wooden form boards used in their construction. In the 1940 Lachen Bridge (below, right), the horizontal form-board lines highlight the thinness of the arch and its thickening at the lower hinges (below, left).



abutments, a smoothly curved arch and a straight roadway deck. In contrast, the Schwandbach Bridge has no stone abutments, its arch is polygonal, and its roadway deck is horizontally curved [see illustration at bottom of page 88]. These innovations give the Schwandbach Bridge a wonderfully original form, making that remote structure in the Swiss wilderness one of the greatest concrete bridges of the century.

Engineering versus Architecture

Maillart's best-known structure is the Salginatobel Bridge, completed in 1930 [see illustration on pages 84 and 85]. The design was based on the hollow-box arch of the destroyed Tavanasa Bridge, but with refinements: Maillart eliminated certain references to older styles, such as the Tavanasa's Romanesque stone abutments. He won the competition for the contract because his design was the least expensive of the 19 submitted—the bridge and road were built for only 700,000 Swiss francs, equivalent to some \$3.5 million today. Salginatobel was also Maillart's longest span, at 90 meters (295 feet), and it had the most dramatic setting of all his structures, vaulting 80 meters (262 feet) above the ravine of the Salgina brook. In

1991 it became the first concrete bridge to be designated an international historic civil engineering landmark.

A few years after Salginatobel was built, though, Maillart criticized his own masterpiece, regretting his decision to round the underside of the arch near the bridge's crown. In his view, this rounding was another unnecessary reference to an older style. He corrected the mistake in his 1933 Felsegg Bridge, which has a "broken arch"—the underside of the arch comes to a point at the bridge's crown.

In 1936 Maillart completed another remarkable bridge, located at Vessy on the outskirts of Geneva. With this bridge, Maillart refined his broken-arch design by moving the two abutment hinges into the span and adding a vertical cut at the center hinge, thus emphasizing the arch's discontinuity [see illustration above]. Even more striking, the cross walls supporting the roadway deck are in the shape of X's. This play with form creates a lively impression, yet the cross walls are also suited to the bridge's structural requirements. Their X shape matches the distribution of the bending moments caused by temperature expansion of the deck, which are largest at the top and bottom of the walls and nearly zero at midheight. Another interesting feature is the series of horizontal lines produced in some of the cross walls by the wooden form boards used in their construction. This pattern of lines on X shapes resembles the painting *Doppelzelt* ("double tent"), by Swiss artist Paul Klee, a contemporary of Maillart's.

Builders commonly use form-board patterns to give texture and decoration to exposed concrete surfaces; the result is sometimes called "architectural con-

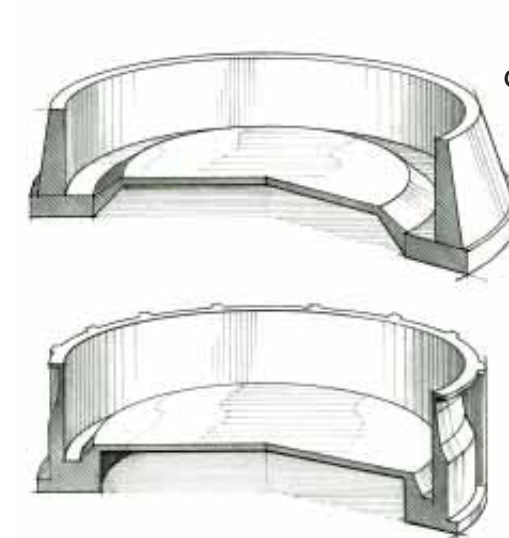


crete.” In 1939, a year before his death, Maillart incorporated form-board patterns into his design of Lachen Bridge on the south shore of the Lake of Zurich. A series of horizontal lines run along the surface of the arch and the vertical walls of the hollow box above it [see illustration at bottom of opposite page]. The pattern highlights the thinness of the arch and its thickening at the lower hinges.

Because Maillart paid so much attention to the appearance of his bridges, he saw no need for the input of an architect to complete his designs. Early in his career he was forced to collaborate with architects on several of his bridges in order to satisfy local officials and, as he called it, their “atavistic antipathy” to his innovations. But Maillart worked alone on all of his most important designs. He was particularly disdainful of the attempts by some architects to give bridges a “monumental” look.

Maillart did appreciate the fact that some architects and architectural writers were perceptive critics of bridge design. Indeed, architects often recognized the high quality of Maillart’s structures before his fellow engineers did. In 1947, seven years after Maillart’s death, the architectural section of the Museum of Modern Art in New York City devoted a major exhibition entirely to his works. In contrast, very few American structural engineers at that time had even heard of Maillart.

In the following years, however, engineers realized that Maillart’s bridges were more than just aesthetically pleasing—they were technically unsurpassed. After World War II, Maillart’s hollow-box arch became the dominant design form for medium- and long-span concrete bridges in the U.S. In Switzerland, professors at the Federal Polytechnical Institute finally began to teach Maillart’s ideas, which then influenced a new generation of designers. One of Maillart’s most prominent followers is Swiss engi-



ORIGINAL PLAN

WATER PRESSURE

BENDING FORCES

MAILLART'S PLAN

WATER PRESSURE

CIRCUMFERENTIAL TENSION

GRAPHICAL ANALYSIS led to Maillart’s design for the concrete bases of two large tanks in St. Gallen, Switzerland. The original plan (*top*) called for thick concrete walls to resist the pressure of the water contained in the structure. But in Maillart’s plan (*bottom*), the resistance comes from circumferential tension in the steel rods embedded in the concrete, thus allowing the walls to be thinner.

neer Christian Menn, who designed many striking deck-stiffened arch bridges beginning in the late 1950s. By the early 1970s American engineers started to build deck-stiffened arches as well.

Viewed from a historical perspective, Maillart fits squarely in the engineering tradition established by John Roebling, designer of the Brooklyn Bridge, and Gustave Eiffel, creator of many impressive bridges and, of course, the Eiffel Tower. For all three men, design came first. They began with the forms or shapes that expressed their visions of structural art; then they used simple analytical techniques to develop their plans. Maillart’s work provides a valuable lesson for today’s engineers: he was able to design stunningly original bridges and industrial structures because he possessed artistic sensitivity, broad construction experience and deep technical proficiency. In the modern art of structural engineering, these three qualities must go hand in hand. SA



FLARING COLUMNS merge smoothly with the concrete slab above them in Maillart’s Filter Building in Rorschach, Switzerland, constructed in 1912. Maillart’s design allowed the columns to support the heavily loaded slab without the need for horizontal beams.

The Author

DAVID P. BILLINGTON has been teaching engineering at Princeton University for 40 years and currently holds the title of Gordon Y. S. Wu Professor of Engineering. He received his bachelor of science in engineering degree from Princeton in 1950 and worked as a structural designer at the firm of Roberts & Schaefer in New York City before joining Princeton’s faculty in 1960. He has published six books, including *Robert Maillart’s Bridges* (Princeton University Press, 1979), *The Tower and the Bridge: The New Art of Structural Engineering* (Princeton University Press, 1985), and *Robert Maillart and the Art of Reinforced Concrete* (MIT Press, 1991).

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the Killing Lakes

*Two lakes in Cameroon are poised to release lethal gas, as they did in the 1980s. Writer **Marguerite Holloway** reports on scientists' efforts to prevent another tragedy*

Mohammed Musa Abdulahi woke one Saturday morning to find he couldn't feel or move his right arm. He remembered he hadn't been feeling well, that he had gone to lie down inside the schoolhouse instead of taking care of the younger students, as he sometimes did. He got up, his arm hanging uselessly at his side, and prodded his friend, who also had come inside to take a nap. The friend jolted awake, cried out for no apparent reason and raced away. Abdulahi started to walk home through his village in northwestern Cameroon and found it horrifyingly silent. The dirt roads and yards of Subum were littered with corpses. People lay unmoving on the ground, as if they had fallen suddenly while in the middle of a stroll or a conversation. The dogs were dead. The cattle were dead. Birds and insects had dropped from the trees.

Abdulahi made his way to his father's house, only to find that his entire family was also dead—his brothers and sisters, his father and his father's two wives. For a moment, though, there was a small hope. He touched one of the babies, and it began to cry. Abdulahi tried to pick it up, but couldn't because of his lifeless arm, so he made a crude sling out of cloth. When he touched the baby again, it too was dead.

"It is terrible to be without a family," he says. "Everything you do, you feel not quite right." Abdulahi tells me his story as we sit on the southern shore of Lake Nyos, the very lake that spewed a cloud of lethal gas on the evening of Thursday, August 21, 1986, killing all 11 members of his family and at least 1,700 other people. The very lake that could explode again at any moment. It is the first time Abdulahi has returned since the disaster—since he spent two days in the coma that somehow saved him—and he is now a tall young man of 29. "It is not that I made a decision not to come back," he says in his calm way. "It is just fate now."

It is indeed strange circumstance that has united Abdulahi and an international team of scientists who have come to Cameroon to study the deadly lake in order to disarm it, if they ultimately can. Earlier this afternoon Abdulahi walked down the mountains from the

CARBON DIOXIDE from deep in Lake Nyos (*below*) welled up in August 1986 and was responsible for killing about 1,700 people and their livestock.



MARGUERITE HOLLOWAY

SUSAN CARLSON





PETER TURNLEY Corbis

town of Eseh to the lake in his tan overcoat, black pants and black-and-white checked shirt. He brought a dapper presence to the shore's chaos of monitoring equipment, raft-building supplies, inflatable boats, tents, coolers, mangy dogs, soon-to-be-cooked chickens, and frenzied, unwashed scientists—and one unkempt journalist—surrounded by their entourage of several dozen local visitors. A day or so earlier a driver on his way to meet the team at Lake Nyos had asked for directions in the city of Bamenda and had procured Abdulahi as a guide. Only a week after he had watched a broadcast about the team's arrival in Yaoundé, the capital, and had wondered how he could become involved, Mohammed Musa Abdulahi found himself camping next to Lake Nyos, taking part in the project.

For the team members, their October 1999 arrival in Yaoundé had also marked a beginning. Since 1986 scientists studying Lake Nyos have sought to rid the lake of the deadly gas that accumulates in its bottom waters before it explodes again and kills thousands more. Degassing the lake is technologically straightforward—and in the context of natural-disaster prevention, easy and cheap. Yet accomplishing this relatively simple task has proved astonishingly difficult. Despite the clear urgency of the problem and the unique opportunity to forestall natural disaster, little has been done to protect the people around Lake Nyos. Politics, lack of financial support (because of the reactive rather than preventive orientation of some funding organizations), and miscommunication have all interfered. But in Yaoundé—despite the persistent and worrisome flickering of some of these same problems—it appeared things were finally about to happen.

Nyos is a stunning lake, surrounded variously by cultivated fields, cathedral-like rock faces and verdant hills. On the afternoon of Abdulahi's arrival it looks gray and glass-flat calm. But in its depths, Nyos is active. It is a crater lake, one formed by a volcanic eruption about five centuries ago that left a plug of magma at the bottom of the crater. This plug cooled and the depression filled with water, 210 meters deep. It is one of many such lakes found the world over in volcanic chains—but one of only two, it appears, that have ever exploded and taken human life. The other one, Lake Monoun, lies just 95 kilometers to the southeast.



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- 1 Cornfields next to Lake Nyos
- 2 Mohammed Musa Abdulahi
- 3 Bridge between Bafumen and Eseh
- 4 Memorial to the Lake Nyos victims in the town of Bafumen
- 5 George W. Kling
- 6 Camp on the southern shore

From deep volcanic activity, carbon dioxide (CO_2) gas rises up until it meets groundwater beneath the lake, dissolves into that water and flows into Nyos, carrying with it minerals, themselves dissolved by the reactive gas. It accumulates in solution, staying separate from the upper layers of freshwater. In most crater lakes the lower water periodically turns over, bringing any gas-rich water to the surface, where the gas diffuses harmlessly into the atmosphere. But Nyos and Monoun do not turn over. The boundary, called the chemocline, between the mineralized, dense deep water and the fresh upper water stays dangerously intact. (Similar conditions prevail at Lake Kivu in Rwanda and the Democratic Republic of Congo, although there is no record of its having ever erupted.)

In these lakes the gas saturates the bottom water until some trigger—a strong wind, a violent storm, cool weather that causes a pocket of upper water to sink, a landslide, an earthquake, no one knows—provokes a bit of deep water to move upward. No longer



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strong-armed by pressure, the carbon dioxide comes out of solution; it bubbles to the surface, pulling more bottom water with it. It is thought that this uprising gains momentum, a few bubbles becoming a stream of bubbles and then, like champagne finally uncorked, the gas-laden water erupts in a great fountain—at Nyos, the jet was 80 meters high—and carbon dioxide fills the air.

A weighty gas, half again as heavy as air, carbon dioxide hugs the ground, suffocating anything in its path. When Lake Monoun exploded on August 15, 1984, 37 people were killed. Lake Nyos, which is larger and deeper, was more devastating. The cloud of gas rolled down the hills at an estimated 72 kilometers per hour, into valleys and villages up to 20 kilometers away. According to George W. Kling—a University of Michigan biologist who has extensively studied both lakes and who is the leader of the team Abdulahi has joined—the last person to die was a girl who, the morning after the explosion, descended into a ravine where the gas hung, heavy and low. Abdulahi thinks he and his friend were saved because they were sleeping in a room that somehow, despite the open door, protected them from the full onslaught of gas. Abdulahi slept for about two days, and because of lying on his right arm for so long was unable to use it for several months. Abdulahi believes

the gas disturbed his friend's mind—an observation that is consistent with reports of disorientation in many of the survivors.

Lake Nyos is clearly poised to kill again, as is Lake Monoun. According to the most recent calculations by Kling and chemist William C. Evans of the U.S. Geological Survey, Lake Nyos contains twice as much carbon dioxide as was released during the explosion (0.4 cubic kilometer today, as opposed to only 0.17 cubic kilometer in 1986). Another explosion could also rupture the fragile dam, or spillway, at the northern end of the lake, and the waters could flow as far as Nigeria—drowning or displacing as many as 10,000 people. Although the area around the lake was evacuated after the disaster and 3,500 or so refugees resettled in safe places, many people are again living nearby, drawn by the land's richness. Cornfields abut the water's edge on the southern side. Cattle graze the hills around the lake under the watchful eyes of their Fulani herders. And in the early 1990s some European scientist released tilapia into the fishless lake in an uncontrolled and unauthorized experiment. The fish thrived, altering the ecosystem in unknown ways and becoming another incentive luring people to the lake. With few resources or possibilities for earning a living, the impoverished people of the area have little choice but to approach the deceptively benign-looking waters of Nyos.

Perhaps fortunately, the enormous difficulty of reaching this beautiful spot keeps outsiders away. Its remoteness, however, also makes it hard to study and degas. Five days after arriving in Yaoundé, we set out for Nyos in four vehicles. Part of the team—Evans; Kling and his assistant, Karen J. Riseng; Minoru Kusakabe of Okayama University and four of his colleagues from various institutions in Japan; Gregory Tanyileke of the Cameroonian Institute for Geological and Mining Research (IRGM) and I—take our places in two rented Nissan Patrols with their drivers. The others, including Tanyileke's IRGM colleagues—Hubert Mvogo, Jacob Nwalal, Paul Nia and Justin Nlozoa—drive two trucks laden with equipment. We travel to Bamenda in comfort, passing logging trucks with some of Cameroon's remaining old-growth forests stacked high on their backs, passing red cocoa beans that smell like vinegar and fluffy

white manioc spread on the side of the highway to dry. We spend the night in a hotel, pick up supplies—including 36 rolls of pink toilet paper for 14 people—and head to the end of the paved road at Fundong. (We later run out of fresh water. We still have toilet paper.)

The single road heading north from Fundong is ghastly and effectively isolates the region around Lake Nyos. It is more a series of vast muddy pits, connected, on a dry day, by an uneven dusty trail, than it is a road. For 13 kilometers we slip and slide and lurch and stick, and the sway bar on one of the Nissans breaks. By late afternoon it is clear that despite Kling's frustration we can't get any farther than the village of Bafumen. Members of the Japanese team wisely find a house to stay in, and the rest of us pitch our tents in a cemetery, right below a memorial to victims of the Nyos disaster. Lake Nyos is just 17 or so kilometers away now, but it seems as inaccessible as Yaoundé. And word about town is that the bridge on the road to Eseh has been washed out.

We start out the next morning with fresh faith. The sway bar had been soldered back together, and the evening's chill softened by Bafumen's supply of warm beer. After repairing the first flat of the day, we reach the bridge. It hasn't been washed out. The left side is, in fact, intact. Only the right side is falling into the river. The entire team descends from the vehicles, and there is much scientific and highly technical muttering about mass and stability and speed and load and distribution, in the midst of which Mvogo jumps in the equipment truck he commands—"The Grandmother"—and speeds her across. By the end of the day we have reached Eseh, spent hours waiting out a downpour, and have set up camp after hiring the entire town to carry, on their heads, all our things—including the hard, heavy suitcases infelicitously packed by team members who thought we would be driving right to the water's edge—the six kilometers down the steep slippery-when-wet path to the lake. In the middle of camp we place a blue crate filled with canisters of oxygen: 10 minutes apiece for just 10 of us. (Some of us initially try to set up our tents on a hill so that we will be safer if the lake decides to explode again. But it proves too difficult, and with a small but nagging fear we pitch below in the main camp.)

The first task the next morning is raft building. After the explosion in 1986

Kling and his colleagues set up a climate station on a raft in the middle of the lake to monitor temperature, wind, sun and rainfall. That station, beaten ragged by the weather, no longer functions, and the raft needs replacing. In addition, the team needs to install thermistors that will hang from the new raft at nine different depths to record changes in temperature—which reflect the movements and chemistry of the lake's waters. They also need to lower probes to measure the carbon dioxide's pressure. Only once these instruments are in place will it be safe to think about a major degassing. Every stage of that operation must be observed to see if it is dangerously altering conditions. So the first order of business is to build a raft sturdy enough to hold the new



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climate station, to anchor the various probes, and, if possible, to provide a large enough platform from which the scientists can drop canisters to collect water so they can measure carbon dioxide concentrations. The Japanese contingent, under the direction of engineer Yutaka Yoshida of Yoshida Consulting Engineer Office in Iwate, Japan, takes charge of building the raft.

By the time Abdulahi arrives in camp two days later, the raft has been completed and the climate station assembled and attached to it. Abdulahi finds room in one of the tents and borrows some clothes for his stay. The following day he helps Evans and Riseng with their work. The thermistors need to be unwound, marked for depth and taped

- 1 Children from Eseh
- 2 The raft is launched
- 3 Climate station atop the raft
- 4 Spillway at the northern side of Lake Nyos
- 5 Hubert Mvogo helps unwind thermistors

firmly together for stability, so Riseng sends her assistants to the far ends of the cornfields with the long wires that will stretch nearly to the lake bottom. Seventeen men are scattered between the bright-green plants, wires draped over their shoulders—one of them, 201 meters away, is barely visible on the horizon of a field. Abdulahi helps Riseng rewind the thermistors and then decides to brave a trip on the lake, where he checks the anchors for the new raft with



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Evans and Tanyileke. The sun is blindingly hot. Some of us sit around camp in a stupor. A Fulani gentleman brings a gift of avocados. The day stretches on.

Abdulahi comes back from the lake. He now has one of the walkie-talkies and has become a field coordinator, helping everyone find what, or whom, they need. We sit on a box of equipment and—between static-pocked demands from the transmitter—talk about his desire for a family. He says he has met a woman he wants to marry and who wants to marry him, but her family has objected. They are hoping for a rich suitor instead of an electrical engi-



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neer, the occupation Abdulahi chose years ago. “Why is this happening?” he asks sadly. “First my family, now a wife.”

With the raft done, the instruments down and water samples collected, Kling and his colleagues have set the stage for the degassing operation that will, with luck, commence this fall or winter. Over the past several years, Kusakabe and Yoshida prepared a \$3-million plan to degas the lakes that was submitted to the Japanese International Cooperation Agency by the Cameroonian government. Their design entails running 12 pipes into Nyos, at three different depths, and allowing the CO₂-laden water to froth up, perhaps at the initial rate of 320 kilometers per hour, to release its gas. They envision three such pipes at Monoun.

This idea has been around, in various iterations, since Lake Nyos exploded. And a version has been tested on both lakes. In 1992 Michel Halbwachs of the University of Savoy secured funding from the French government and the European Community to do a preliminary degassing test in Monoun. Halbwachs and his colleagues, Tanyileke among them, lowered a five- and a 14-centimeter-diameter pipe and, using a motorized pump, sucked up some bottom water. Because of the pressure differential, a self-sustaining fountain of gas-rich water gushed up in both pipes, and carbon dioxide diffused away. They were able to close valves in the pipes to shut off the release.

The success of the Monoun project led to a similar effort in 1995 at Lake Nyos. With money from Gaz de France, Halbwachs and others lowered a 14-centimeter-wide, 205-meter-long pipe. Things did not go as smoothly as they had at Monoun, however, and after the fountain started, the pipe rose, terrifyingly, from the bottom. Fortunately, no explosion was triggered, and the experiments suggested degassing was feasible.

Halbwachs had a different plan from Yoshida and Kusakabe's. His entailed only five pipes for Nyos and a remote on-off switch that could be controlled via satellite from France. Although the scientists met in Yaoundé in October to hash out their disagreements, and appeared to do so, the conflict emerged a day later at a public meeting with members of a newly formed Cameroonian interministerial committee on degassing. Halbwachs presented his five-pipe plan, and Kusakabe presented the 12-pipe

version. The ministers focused on the discord, and for a short and wrenching time it looked as though the entire project was going to be derailed.

Ultimately, Henri Hogbe Nlend, minister of scientific research and technology and head of the committee, reassured everyone that the disagreements were petty. "Any number they give now is false, everything is an estimate," he said forcefully. "The technology that they have explained will keep evolving." No one, he added, should expect

them that they have not been able to get money to degas them. In 1992, for instance, a meeting on degassing was organized with the support of UNESCO and the United Nations Development Program. But neither institution put forth money for the actual project, Kling says. The scientists have tried some other channels with little success. Kling and a colleague tried to interest oil companies—which have a powerful, lucrative presence in Cameroon. No luck. And the same year as the U.N. conference,

plumbed, but the larger issue is that many aid organizations are responsive, not preventive. Many people within this community have emphasized the dangers of this approach. But OFDA's Neal says it has only lately begun to change and points to recent mitigation efforts at AID and the Federal Emergency Management Agency. "I think at AID there has been a learning process and a cultural shift in the past few years that mitigation is increasingly the important way to approach problems and that by running in after an earthquake or merely saving bodies and providing first aid, we don't do anything for the long-term problem," she says.

It is in great part because of Neal's interest in Cameroon and its lakes and because of her strong belief in mitigation that \$433,000 finally came through for Kling and the team last fall. The OFDA grant was triggered by the eruption of Mount Cameroon in the spring of 1999. The office sent John P. Lockwood, formerly of the U.S. Geological Survey, who had studied Lake Nyos, to determine the extent of the danger. After meeting with U.S. Embassy representatives in Yaoundé and Cameroonian scientists

"We, the scientists, are still wondering, was it enough to just send reports to everyone?"

the architects of a cathedral to supply specifics in the face of such a great enterprise. Uniting the various ministries behind the operation had been a monumental task. Without their combined support, the roads would not be improved, the areas around the lakes would not be evacuated, and the Cameroonian military would not be present at the degassings with oxygen tanks in case of an explosion. Minister Nlend, apparently, was not going to let some minor grievances thwart the project. And all the scientists are collaborating again.

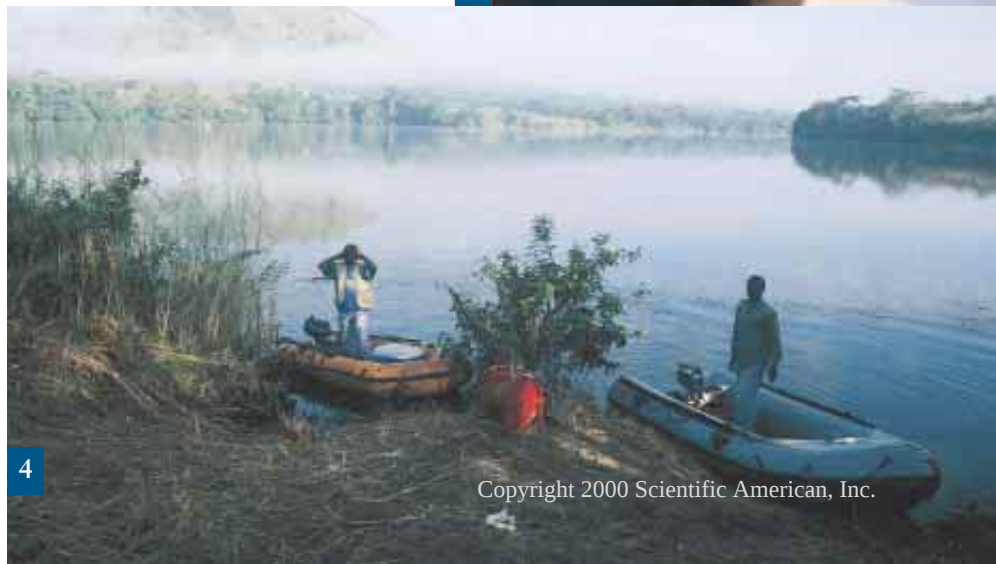
The disagreement was atypical for a community that has been largely collaborative for more than a decade. The debate is partly the result of scientific disagreement, but in truth, the differences in designs are negligible. It appears to have resulted more from a lack of communication among the researchers about, or during, their efforts to get funding. Halbwachs felt excluded from work for which he had laid the foundation. The others say they were pursuing funding catch-as-catch-can, thinking all along that Halbwachs would work with them. "We have always assumed that anyone who cares about these lakes is working together," Kling says.

Securing funding for the project has indeed been a desperate venture. Here are two lakes that will explode, thousands of people at risk and an easy solution that could cost as little as \$1 million. And yet. Although various researchers have received support from their governments or their institutions to study the lakes, it has frustrated many of

Kling appealed to the U.S. Agency for International Development (AID) and was refused because at that time the agency was not inclined to fund projects in Cameroon. After helping the victims just after the disasters, "AID had disengaged somewhat," explains Christina Neal, a geologist in the agency's Office of Foreign Disaster Assistance (OFDA). "Cameroon had a problem with democracy and good governance."

Kusakabe's efforts to get money from the Japanese International Cooperation Agency came to naught as well. Some say the Japanese government wasn't as committed to the degassing as it was to other projects in Cameroon. Others say that the Cameroonian government, which had to rate the project as the number-one aid priority to receive funds, couldn't reach consensus and that one minister favored a well in his village instead.

The politics may never be fully





and ministers, he concluded that if OFDA really wanted to help Cameroon, it should do something about the lakes.

Although the degassing seems to be on track now, many researchers still feel somehow guilty—as though they should have done something more and because they didn't know exactly what to do. Tanyileke worries that he and the others were not clear enough about the danger—at least not in a way that moved anyone to act. “We, the scientists, are still wondering, was it enough to just send reports to everyone?” says Tanyileke one late afternoon at Nyos. We are sitting on a cooler in the sun, and the weight of the heat even late in the day is leaden, stupefying. “They weren't strong enough to make them sit up.”

As we talk, a nine-person delegation from Nyos village arrives. They are arrayed in finery—hats, umbrellas, bright robes—and bring a letter from their chief, Fon Tang-Nembong: “Our dear visitor we are very very happy to see you

people here in our lake. We here to say will come to you all.” Tanyileke describes what the team is doing and why. “An explosion could happen any day,” he warns, adding “if we are doing anything that is going against your traditions, you must tell us.” All the members of the team, but Tanyileke and Evans in particular, try to explain their work to the people they meet.

Such communication is crucial for many reasons, not just for good relations. It encourages people to be wary of the seemingly safe lake. It fosters scientific awareness that Tanyileke hopes will contribute to making Nyos a research center once the lake is degassed. And, finally, it helps to quell an unhelpful rumor. The rumor began, according to anthropologist Eugenia Shanklin of the College of New Jersey, when a priest who visited the devastated villages described the scene as resembling the aftermath of a neutron bomb. And so the bomb story was born. One version has Americans and Israelis detonating the device to get to diamonds under the lake. Another has a blond-haired Peace Corps worker placing the bomb so that Americans could live in the region.

The rumor rankles the team—and the Peace Corps and the U.S. Embassy in Yaoundé and, perhaps, the Israeli medics who provided disaster relief in 1986—and could interfere with evacuation efforts during the degassing if some of those same groups participate. But Shanklin finds the emergence of a modern myth intriguing—just as intriguing as the region's ancient tales. One of the legends suggests that what happened at Nyos and Monoun is not without precedent: a myth of the Kom people describes a lake that suddenly exploded and decimated a tribe.

For their part, the delegation from Nyos doesn't seem suspicious of the team's work. “We are very happy for your coming here,” Tamaki Cheteh says. “Everyone in Nyos is sick from this gas.” And then, in a request as remarkable as Abdulahi's foray on the lake, a member of the delegation asks to taste the water that killed many of his relatives. With Abdulahi standing nearby, Tanyileke offers him some of the carbonated water collected right near the bottom. Everyone gathers around, and, in turn, they drink from the depths of their lake.

Readers interested in supporting the effort can send contributions to the Cameroon Degassing Project, Dept. of Biology, University of Michigan, 830 N. University, Ann Arbor, MI 48109-1048.



- 1 Children hold thermistors at Lake Monoun
- 2 Gregory Tanyileke
- 3 Villagers from Nyos drink from their lake
- 4 Lake Monoun

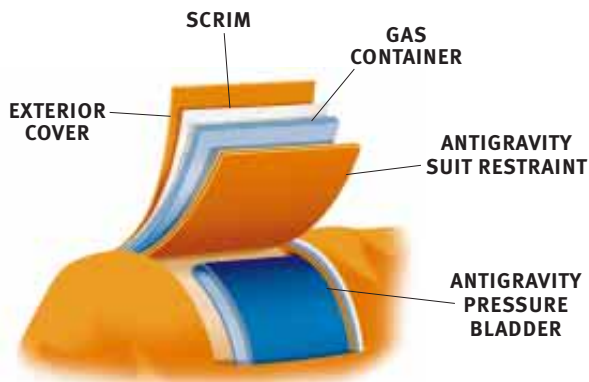
Escape and Survival

After the success of the first four shuttle test flights, space-bound astronauts sported sky-blue coveralls and an oxygen mask that was hardly more than a glorified motorcycle helmet. Thanks to the ships' pressurized crew cabins, these Americans became the first to fly without the hot, bulky pressure suits that their predecessors wore. In an emergency, they expected to land the spacecraft at the nearest acceptable runway—they had no means of escape. For missions 5 through 24, this minimalist philosophy sufficed.

After the shocking explosion of *Challenger* in 1986, the National Aeronautics and Space Administration instructed its engineers to design an escape plan for future crews. They also reinstituted the use of a pressure suit, which protects the wearer from fire, immersion in cold water and sudden cabin decompression. (The suit automatically takes in or lets out air depending on outside air pressure.) So were born the blazing, sunset-orange outfits that astronauts now wear on liftoff and reentry. The suit's garishness is a survival feature, every bit as much as the associated parachutes, life raft, flare guns and other gear: the color is meant to draw the eye of searchers scanning the ocean waves for a bobbing astronaut.

David Clark Company in Worcester, Mass., manufactures the suits, officially known as advanced crew escape suits. No mission has experienced an emergency that required use of this escape gear, but the U.S. Navy, which provides the parachutes, jump-tests the suits every two years.

—Sarah Simpson, staff writer



ESCAPE SUIT MATERIAL includes a gas container made of breathable Gore-Tex and restrained by a canvaslike Nomex cover. The specialized Gore-Tex holds pressurized air inside the suit and allows water vapor to escape; the Nomex provides flame and abrasion protection. During return to gravity, astronauts also wear an antigravity suit, which squeezes the legs to keep blood from pooling in them.



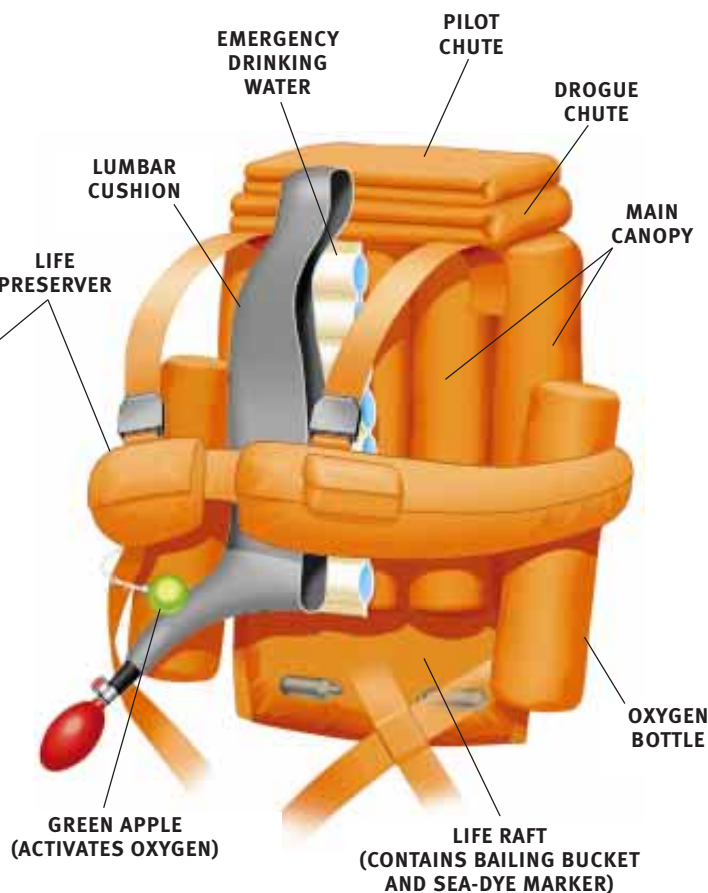
SHUTTLE BAILOUT is a last resort to be used only if landing becomes impossible. Ideally, the astronauts equalize cabin pressure to that of outside air and remove their lap belts at 40,000 feet. A designated crew member blows the escape hatch at 30,000 feet, and each astronaut hooks a D-ring on the suit to an 8.5-foot, telescoping escape pole. As each astronaut slides clear of the craft, forces on the D-ring start the parachute sequence. When the main canopy exits the pack, it activates a SARSAT locator beacon. The parachute is released automatically at splashdown, a life preserver and yellow life raft inflate, and green sea dye can be deployed.

SURVIVAL-GEAR POCKET contains light-sticks, strobe light, signal mirror, flare guns and motion sickness pills.





PARACHUTE PACK forms the back of the astronaut's seat in the shuttle, but it stays strapped to the astronaut in case of a bailout. Engineers designed the pack and harness with the incapacitated wearer in mind: the parachutes, life preserver and life raft all deploy automatically.



DID YOU KNOW ...

- Before NASA engineers invented the escape pole, tractor rockets were the bailout method of choice. The astronaut would lie flat on his or her back and attach a lanyard on the suit to a rocket. When the rocket blasted through the escape opening, it would yank the astronaut out with it—at a force 12 times that of gravity.
- What about the crew member who has been living weightless in a space station so long that his or her muscles have turned to jelly? To prepare for such a situation, shuttle crews practice bailing out while assisting a corn-filled suit that emulates a heavy, limp astronaut.
- The first version of the crew escape suit was much hotter and bulkier than the current incarnation, because nonbreathable urethane-coated nylon constituted the layers that are now made of Gore-Tex.

PCR at Home

Shawn Carlson explains how you can carry out the polymerase chain reaction in your kitchen

Mark my words: one day Eva Harris will win the Nobel Peace Prize. This visionary professor at the University of California at Berkeley will certainly deserve such recognition for her work, which could save countless lives. Harris develops inexpensive ways to conduct sophisticated biomedical tests and then brings that technology to people in the developing world. By providing the right equipment and training to local public health workers, she is building epidemic-

logical firewalls around disease "hot spots." These preparations are now helping to contain outbreaks before they grow into epidemics.

In 1998 Harris founded the Sustainable Sciences Institute in San Francisco to carry out this mission, and already her group has achieved some stunning successes. As part of that effort, Harris recently published *A Low-Cost Approach to PCR* (Oxford University Press; ISBN: 0-19-511926-6), which is the definitive manual on cost-conscious biotech. Though intended for

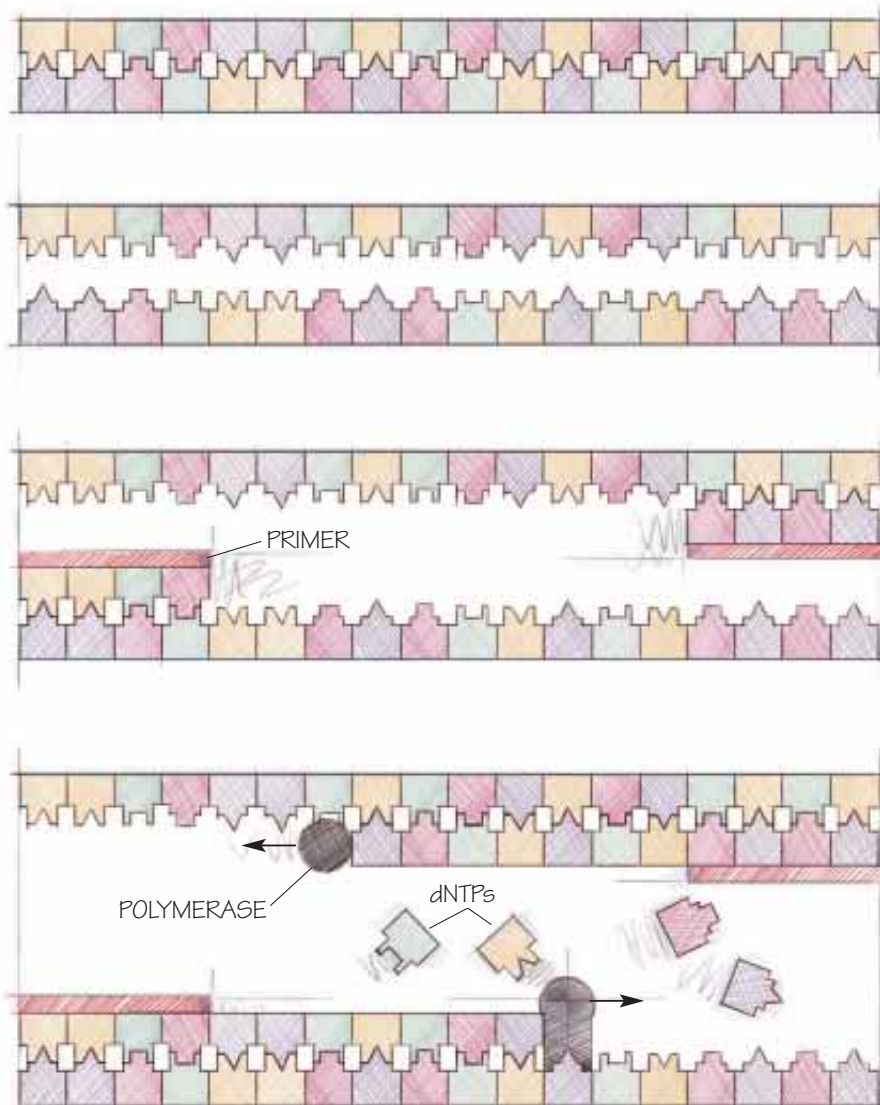
health professionals, this book is a boon for amateurs working on a budget. It explains how anyone with a bit of inexpensive equipment can carry out the polymerase chain reaction (PCR), a technique for generating large quantities of DNA.

The PCR method unzips a DNA double helix into two complementary strings, which are immersed in a soup of DNA building blocks. The proper experimental conditions induce these constituents to assemble two new copies from what was originally one DNA molecule. The steps involved take just a few minutes. And repeating the procedure doubles the number of copies each time. So 30 cycles of PCR produce a billion-fold increase of the targeted section of DNA, "amplifying" what might begin as a single molecule into enough material for easy examination.

Amateur scientists can do PCR at home, but the exercise is quite challenging. For one, the very sensitivity of PCR means that this technique is extremely vulnerable to contamination: a single wayward cell could render your experiment meaningless. The serious experimenter should purchase Harris's book and a good textbook on biochemistry. To get you started, this column describes a demonstration of PCR that avoids most of the pitfalls. And the Society for Amateur Scientists can supply the materials that are difficult to obtain.

First, you will need some of your own DNA and several sterile Pyrex test tubes with rubber stoppers—or better yet, some plastic microcentrifuge tubes with built-in caps. You can reduce the risk of contamination by washing your glassware and working surface with bleach and by wearing latex gloves at all times. To collect the

GENE AMPLIFICATION begins with double-stranded DNA (a). Heat parts the strands (b), and short segments of DNA (primers) attach to specific locations (c). The polymerase enzyme attaches DNA building blocks (dNTPs, shown in yellow, green, pink and purple) sequentially to each strand, forming two new strings of DNA that complement the originals. Repetition of these steps doubles the amount of DNA present after each iteration.



DNA sample, gently scrape the inside of your cheek with a sterile cotton swab, then slosh the tip around inside a clean tube filled with a few milliliters of distilled water. Gently boil the water for two minutes to rip open the cell walls and release your genetic blueprint. The solution will now contain a few DNA fragments, as well as other large molecules and sundry leftovers from the ruptured cells.

Let this biological broth cool and then, if you can, use a blender-centrifuge [see *The Amateur Scientist*, January 1998] to separate and remove the larger cellular debris. Some of the dissolved molecules can interfere with PCR, so practitioners usually dilute the solution by factors of 10 and 100 to reduce the concentration of any troublesome ingredients. Once you have made these preparations, keep your samples packed in ice until you are ready to use them.

The high price of materials leads even professionals to use fantastically tiny amounts of the various reagents, often one microliter or less. Dishing out such small quantities typically requires a calibrated pipetting tool (such as part no. S346503 from Fisher Scientific, www.fishersci.com, \$219; you'll also need the disposable pipette tips, part no. S346501, which cost about \$30 for a set). But you can instead employ translucent plastic coffee stirrers. Just dip the straw into the solution to the appropriate depth and cover the end with your thumb as you transfer the contents. The set of white stir sticks I purchased from my grocery store cost less than two cents apiece and yet deliver about 70 microliters for each centimeter of length. I found that I could transfer 70 microliters of liquid very consistently (to within about 4 percent), and I could dole out as little as five microliters with only about 40 percent error.

The recipe for PCR soup given above consists of a buffer, two primers, a polymerase enzyme, DNA building blocks (called deoxynucleotide triphosphates, or dNTPs) and magnesium chloride. The buffer keeps the reaction at a constant pH. The primers are short fragments of unzipped DNA that bond to the specific sites on human DNA and define where the copying begins and ends. The polymerase enzyme assembles the DNA building blocks, and the magnesium in the solution helps keep the reaction going.

Make up several tubes with these ingredients. Be certain that one tube contains only the reagents; that is, do not add any of your DNA to it. You will run

this one through the amplification steps to serve as a negative control: no DNA should show up in this vial in the end.

Begin the PCR cycle by splitting the DNA with heat. At about 94 degrees Celsius (201 degrees Fahrenheit), the double helix unravels in roughly a minute. You should keep your test tubes stoppered (or your microcentrifuge tubes capped) to prevent evaporation. Next, lower the temperature to about 60 degrees C (140 degrees F) for about 90 seconds. This step induces the primers to bond to the sepa-

PCR Soup

To a clear and sterile test tube, add:

100 SPU's (smallest possible units) of distilled water

15 SPU's of buffer

8 SPU's **exactly** of magnesium chloride solution

5 SPU's of each of the four dNTP's

3 SPU's of β -globin primer 1

3 SPU's of β -globin primer 2

1 SPU of polymerase enzyme

1 drop of mineral oil (prevents damage to polymerase on freezing)

Freeze unused portion to save for later use.

RECIPE FOR PCR SOUP requires many ingredients mixed together in the specified relative proportions, but only the concentration of magnesium chloride is truly critical.

rated DNA strings. Then raise the temperature to 72 degrees C (162 degrees F) for another 90 seconds, allowing the heat-hardy polymerase (an enzyme that comes from a bacterium native to hot springs) to build the new copies.

The three heating steps can be simply carried out by arranging three hot-water baths and transferring the tubes among them. I just put pots of water on my stove and monitored their temperatures using candy thermometers. It took three hours to shepherd my samples through the baths 30 times. I used a thermocouple inside one of my test tubes to check how quickly the solution reached the proper temperature (one to two minutes); tiny microcentrifuge tubes will equilibrate much faster.

You should end up with loads of DNA molecules, which you can sort by size using gel electrophoresis [see *The Amateur Scientist*, December 1998]. During my tests, I ran three dilutions and one negative control. A more sophisticated researcher would also include a calibration solution that contains DNA fragments of known lengths. Comparing results with the calibration solution makes it easy to gauge the size of the amplified DNA.

After running my electrophoresis gel at 54 volts (generated with six nine-volt bat-

teries) for an hour, I stained it with a dilute solution of ethidium bromide—a nasty mutagenic chemical, which can be absorbed directly through the skin, so take great care not to get any on yourself. Ethidium bromide bonds directly to DNA and fluoresces when illuminated with ultraviolet (UV) light. I darkened my bathroom and used an ordinary (long-wave) black light to observe the faint lines of amplified DNA. Experimenters using a short-wave UV light will see much brighter lines. These so-called transilluminators

cost \$195 from Fisher Scientific (part no. S45157). But remember that when working with short-wave UV, you must wear UV-protective goggles (such as part no. S47733 from Fisher Scientific, \$7) whenever the light is on to avoid damaging your eyes. If you have any doubts about how vigilant you can be, just stick with an ordinary black light.

The ability to do PCR at home opens vast new territories for amateur exploration. If you get good at applying this technique, you might even be able to help the Sustainable Sciences Institute stem the spread of disease. In any case, I urge you to find out more about this wonderful group, which I am sure will eventually receive the widespread praise and support it merits. It took the Nobel committee almost three decades to award the prize to the French humanitarian organization Doctors Without Borders. I just hope that Eva Harris and her colleagues will not have to wait so long. 

To learn more about the Sustainable Sciences Institute, direct your browser to www.ssilink.org, call 415-431-2410 or write to 474 Valencia Street, Suite 120, San Francisco, CA 94103. For more information about this and other projects for amateur scientists, surf over to the Web site of the Society for Amateur Scientists, www.sas.org, and click the "Forum" button. As a service to readers, the society is offering a PCR kit containing all the necessary chemicals, as well as latex gloves and containers to hold your PCR samples. The cost is \$40. Because the ethidium bromide included is a mutagen, this kit will be sold only to adults. The society can also supply an electrophoresis kit for \$60. You may call the society at 619-239-8807 or write to 4735 Clairemont Square PMB 179, San Diego, CA 92117.

Knotting Ventured...

Ian Stewart shows how pieces of string can illustrate the principles of symmetry

In the past century the study of knots has become a major area of mathematical research. Knots embody one of the big questions in topology: What are the different ways to position one geometric form inside another? In the case of knots, the two forms are a circle—which can be represented by a closed loop of string—and the whole of three-dimensional space. As far as topologists are concerned, a knot is a circle that has been embedded in three-dimensional space in such a manner that it cannot be disentangled by continuously deforming the space around it.

This description is somewhat removed from everyday experience: in the real world, bits of string have ends, and when you try to untie a knot you deform the string, not the space around it. Although the topological definition captures the “knottiness” of knots, other aspects do

not reduce so well to a topological formulation. A clear case in point is the problem of knotting two pieces of string together to form a single, longer piece. The main requirement is that the knot should not slip if you pull on the ends of the string. Surface friction and the material from which the string is made come into play, so the task requires a different approach.

Mathematicians have risen to the challenge and developed the beginnings of a theory for such knots. Conceived by Roger E. Miles of the Australian National University in Canberra, the theory is explained in his unorthodox book *Symmetric Bends* (World Scientific, 1995). “Bend” is the word used by sailors for a method of knotting ropes together. Miles’s primary aim is to classify the geometry of bends in a systematic way, making it possible to search for new ones with desir-

able properties such as resistance to slippage under tension.

The simplest and best-known bend is the reef or square knot [see illustration on opposite page]. In the illustrations here, one string is colored orange, the other blue. Each string has a “free” end—the stub protruding from the knot—and a “standing” end, which represents the main part of the string and is indicated here by a faded line. The diagram of the reef has two types of crossings: blue-over-orange and orange-over-blue. In more complex bends, there may also be blue-over-blue and orange-over-orange crossings.

The reef is often confused with the granny knot. Both types of bends can be transformed into conventional knots simply by connecting the free and standing ends of each string. (In traditional knot theory everything is joined into loops.) Conventional reef and granny

FLEMISH BEND

REVERSAL

CHAMELEON

MIRROR IMAGE

REVERSAL OF MIRROR IMAGE

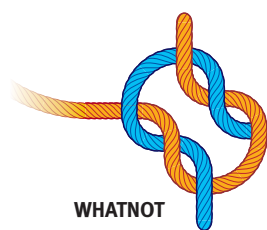
FLEMISH BEND has three variants: reversal, mirror image, and reversal of mirror image (left). The reversal diagrams have been flipped 180 degrees around their midlines. All four bends are centrosymmetric. A fifth bend, the chameleon (above), is topologically equivalent to the other four but rotationally symmetric.



REEF OR
SQUARE KNOT



GRANNY KNOT



WHATNOT



THIEF KNOT



GENERALIZED
THIEF KNOT

FOUR ELEMENTARY BENDS (top row) have few crossings, so they can be easily pulled apart. The generalized thief knot (above) is more secure because it has more crossings.

knots, however, have no close variants, whereas there are two additional bends that are quite similar to the reef and granny, differing only in the choice of which end is free. These are the whatnot and thief knots.

These four elementary bends are the ones with the simplest diagrams—that is, the fewest crossings. Friction, which prevents the strings from sliding out of the knots, is to some extent generated at the crossings, and intuitively we would expect more complex bends to be more secure. But this is not always the case. The security of the bend also depends on how the sequence of crossings fits together in three dimensions. All four elementary bends are highly insecure and tend to come undone if the strings are pulled or otherwise disturbed. The way they come apart is instructive: one string straightens out, though perhaps not completely, and then slides through the loops in the other string.

The elementary bends also have the appealing property of symmetry. If the reef knot diagram is given a diagonal flip—rotated 180 degrees around an axis consisting of the diagonal from the diagram's lower left to the upper right—the same diagram appears, except that the colors (orange and blue) are swapped. The same goes for the granny knot. The whatnot diagram has rotational symmetry: it looks the same, except for color, if it is rotated 180 degrees around an axis pointing vertically out of the page. And the thief knot is centrosymmetric: if you perform a central inversion on the diagram, mapping every point with the coordinates x , y and z to a point with the coordinates $-x$, $-y$ and $-z$, it will look the same as the original, except for color. You can observe these symmetries firsthand by tying the bends with real string. Be sure to tighten them carefully and evenly.

Based on the three types of symmetry just described—diagonal flip, rotation and central inversion—Miles has developed a formalism for studying symmetric bends and even inventing new ones. For example, generalizing the thief knot cre-

ates an entire family of bends [see illustration at right]. In addition, three more symmetry operations can be performed on bends in three-dimensional space. The first is mirror image: on a two-dimensional diagram, you can see the effect of this operation by reversing the crossings at every intersection. The second is color interchange, which is simply swapping the orange and blue colors. And the third is reversal, which involves interchanging the orange standing and free ends and at the same time interchanging the blue standing and free ends.

The prize specimen of symmetric bends is the rewoven figure-of-eight bend, also known as the Flemish bend. The first four illustrations on the opposite page show the bend, its mirror image, its reversal, and the reversal of its mirror image. All four bends are centrosymmetric. The fifth illustration shows a bend with a different symmetry: it is rotationally symmetric. Yet all five bends are topologically equivalent—that is, each one can be transformed into another by simple manipulations. The easiest way to see this is to manipulate the fifth bend, which Miles calls the chameleon, into each of the others. I'll leave you the fun of finding out how.

Miles's book includes a catalogue of 60

symmetric bends. But is there an optimal bend for tying two lengths of string together? Miles's answer is, "Not really." Resistance to slippage or tugging is not the only criterion for a good bend; other desirable features include ease of tying and untying, the ability to adjust the bend to make the free ends longer or shorter, and an aesthetically pleasing appearance. At the end of his book Miles invites readers to inform him of their own discoveries, which he might include in a future edition. (His address is RMB 345, Queanbeyan, NSW 2620, Australia.) Writes Miles: "The inventor of a new knot has the prerogative of naming it! In a way, it's like discovering new comets or novae."

SA

READER FEEDBACK

In response to "Most-Perfect Magic Squares" [November 1999], Thomas R. Hagedorn of the College of New Jersey sent me two papers about magic rectangles published in the journal *Discrete Mathematics* (Vol. 207, Issue 1-3, September 28, 1999). A magic rectangle is an m -by- n array of the integers ranging from 1 to the product of m and n . The numbers in each row add up to the same sum, as do the numbers in each column, but the row sum is not necessarily equal to the column sum. The diagonals are ignored. Mathematicians have long known that magic rectangles exist when m and n have the same parity (that is, when they are both even or both odd), provided that they are bigger than 1 and are not both equal to 2.

Hagedorn generalizes this idea to higher dimensions, showing that if all the sides of a multidimensional array of integers are even—which is true, for example, of a 2-by-4-by-6 array—then a magic rectangle must exist. The odd case is much harder to prove. It is not even known whether a 3-by-5-by-7 magic rectangle exists. So here is my challenge to readers: Can you put the numbers 1 through 105 into a 3-by-5-by-7 grid so that all horizontal rows have the same sum, all horizontal columns have the same sum, and all vertical columns have the same sum? These three sums may (must!) be different.

—I.S.

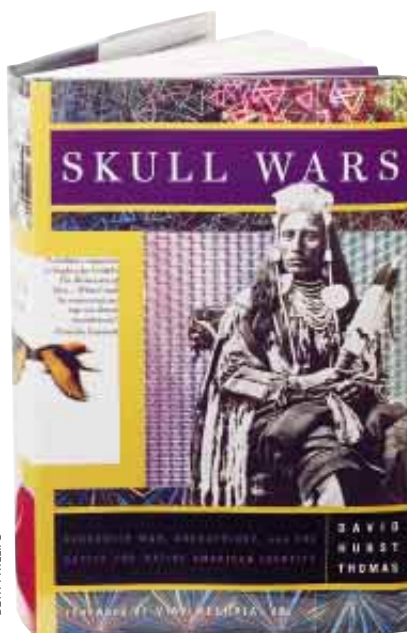
Whose Past Is It, Anyway?

David Hurst Thomas issues a wake-up call to his fellow archaeologists

Just four years ago the 9,500-year-old skeleton now called Kennewick Man eroded from the banks of Washington State's Columbia River and embarked on a final journey that would make him archaeology's cause célèbre. Five Northwest Native American tribes claimed the remains, under a 1990 law, with intent to reinter them. Eight anthropologists sued the federal government to block the bones' return and release them for study—they might reveal intriguing clues about America's human past.

As the legal and political battle to possess Kennewick Man continues, esteemed archaeologist David Hurst Thomas lets loose his own salvo—aimed squarely at his scientific colleagues. Much more important than what Kennewick Man can tell us about the past, Thomas argues, are the implications of his case for archaeology's future. Kennewick Man merely marks a current, contentious example of an enduring conflict for control, in which, Thomas asserts, "The American academic community—led by grave-digging archaeologists—has robbed the Native American people of their history and their dignity." *Skull Wars* issues an overdue wake-up call.

Scenarios for the peopling of the Americas have garnered attention lately in news and science magazines, but *Skull Wars* largely dispenses with distant prehistory to focus on recent history. Much of the book consists of a comprehensive and sobering recounting of how American archaeology developed alongside—and often perpetuated—Native American repression. A curator at the American Museum of Natural History in New York City, Thomas profiles several key 19th-century thinkers who contributed in some way to the ongoing conflict. Samuel George Morton's attempts to correlate skull sizes with race and intelligence prompted looting of Indian graves and promoted manifest destiny. Lewis Henry Morgan erected a ladder of social evolution that placed Native Americans somewhere between upwardly mobile savages and midlevel barbarians. After writing a Ph.D. thesis on the color of seawater, German geographer Franz Boas



Skull Wars: Kennewick Man, Archaeology, and the Battle for Native American Identity

by David Hurst Thomas

Basic Books/Peter N. Nevraumont,
New York, 2000 (\$25)

fathered an anthropology based on biology, culture and language and replaced Morgan's racist scheme with a perspective of unique cultures. Frank Cushing's uninvited immersion in Zuni society made him the first anthropologist to live with study subjects and to attempt linking oral traditions with archaeological traces.

In the 20th century, Thomas writes, as the chasm widened between anthropologists and those Americans they wished to study, the depth of human antiquity on the continent became clear. No sooner had physical anthropologist Aleš Hrdlička declared in the July 1926 issue of this magazine that "not a scrap of bone or implement" supported claims for ancient Americans, news came of an elegant stone spear point found beside fossilized ribs and backbones of an extinct bison at Folsom, N.M. Hrdlička's doubt lingered, but several experts confirmed the evidence for a massive bison butchery by Pleistocene Paleoindians nearly 11,000 years ago. Slightly older artifacts soon appeared, doc-

umenting an even earlier Clovis culture.

Thomas digresses briefly to discuss the recent apparent breaking of the "Clovis barrier" by Monte Verde, a Chilean campsite that pushes human presence in the Americas back to 12,500 years ago. Data from genetics, linguistics, and studies of artifacts have created a situation now where "almost everything relating to the First Americans seems to be up for grabs."

In such heady times, however, scientists must play by new rules. Political developments have dragged prehistorians out of a privileged past and into the present, where Native Americans increasingly wield the authority to determine what aspects of their past will be studied, who will study it and by what methods. The turning point in the power struggle came in 1990, when Congress passed the Native American Graves Protection and Repatriation Act (NAGPRA).

NAGPRA aims to redress past wrongs by requiring museums to inventory collections of bones and artifacts and to assist direct descendants who choose to reclaim these objects. What one museum archaeologist calls the law's "heart, soul and Achilles' heel" is the concept of cultural affiliation: determining a connection between disputed objects and a present-day Native group. Sometimes no doubt exists about who deserves physical and cultural remains. In May 1999, for instance, after seven decades nearly 2,000 skeletons and sacred artifacts were returned to Pecos Pueblo in New Mexico to be reburied. But determining affiliation farther back in time becomes challenging at best. Thomas declares: "With the Kennewick find, archaeologists' worst fears about NAGPRA were realized—that the 1990 legislation would be stretched into deep time, thereby preventing science from studying remains that were not affiliated with any modern tribe."

Ancient skulls and skeletons have already been returned to tribes in Idaho and Minnesota. Kennewick Man's ultimate resting place will most likely be determined this year. In January the Department of the Interior controversially con-

cluded that the skeleton is legally Native American under NAGPRA and subsequently proposed DNA testing to investigate specific cultural affiliation. Experts examined the bones in April for their potential to yield genetic material.

Kennewick Man constitutes one possible outlook for post-NAGPRA anthropology. But Thomas tells of another discovery made the same month of similarly ancient human remains from an Alaskan cave. In that case, a good rapport already existed between archaeologist Terry Fifield and the local Tlingit and Haida elders. The tribes decided to learn more about these bones and artifacts, and members became active players in the excavation. Or there's the example of Phillip Walker, a physical anthropologist who worked with the Chumash people to design an underground ossuary at the University of California at Santa Barbara, where research on tribal remains proceeds in a respectful setting. Thomas hopes for a future marked more by such cooperation than by contention, with Native views informing the questions that archaeological techniques try to answer.

The challenge will be reconciling widely divergent cultural perspectives in a way that enriches knowledge about the past. The "stridently anti-science" views of Native American scholar Vine Deloria, Jr., illustrate the dilemma. In his foreword to *Skull Wars*, Deloria refers to the idea of the first Americans arriving across the Bering Strait before 12,000 years ago as "a myth with little to recommend it," and Thomas quotes him ridiculing this "triumph of doctrine over facts." Lines of scientific evidence dispute the timing and other details of the journey, but Deloria's "facts" stem from oral history, which tends to conclude simply that Native Americans have always been here. Thomas suggests that Deloria accepts lower standards for evidence from oral history than he demands from scientists. Can, or should, American archaeology blend mythology with methodology?

Thomas offers no clear answer. After the sweeping historical account, his section on NAGPRA and potential resolutions of the Skull Wars comes across as abrupt. One wishes for more about the changing nature of archaeology—for some assurance that each new discovery won't follow the path of Kennewick Man. But that's a story still unfolding. ■

BLAKE EDGAR is a senior editor of California Wild magazine at the California Academy of Sciences and co-author with Donald Johanson of *From Lucy to Language*.

THE EDITORS RECOMMEND

NILES ELDRIDGE'S *The Triumph of Evolution: And the Failure of Creationism*. W. H. Freeman and Company/Peter N. Nevraumont, New York, 2000 (\$24.95).

What drives the creationists? As Eldredge puts it, "The argument is simple: the Bible says that 'mankind' was created in God's image. If that is not true, if instead we are descended from the apes, then there is no reason whatsoever to expect humans to behave in a godlike, moral fashion." And so the primary aim of the creationists is political: "to see that evolution is not taught in the public schools of the United States." Eldredge, a curator of invertebrate paleontology at the American Museum of Natural History in New York City, holds that "the integrity of science education in the United States and abroad is directly threatened by such nonsense." With this effect: "Pretending to young minds that we cannot tell the difference between good science and bad, between the real and the bogus, not only sends a horribly distorted message about the very nature of science, but also makes evident to most students that adults don't care much about the truth."

Eldredge deplores this situation and envisions a better one. We face, he says, "a true millennial issue: a set of environmental problems besetting humanity at the year 2000, but a problem in which science and religion, instead of acting as enemies, stand a good chance of working together within the larger body politic to effect some truly positive measures."

EDWARD HARRISON'S *Cosmology: The Science of the Universe*. Second edition. Cambridge University Press, Cambridge, England, 2000 (\$54.95)

Don't say we didn't warn you: this book may well blow your mind. Of course, bogged brains are an occupational hazard in cosmology, the branch of astrophysics that studies the universe on its very largest scales. Practitioners of the field talk about the origin of time and the possibility of parallel universes in the way most people make shopping lists. But why should they have all the fun? This long-awaited update to Harrison's classic textbook is ideal for those who have exhausted the beginners' accounts and want to dig deep into the science and philosophy.

Harrison offers fresh ways to think about basic principles, and he strolls down long-forgotten byways that give such richness to the subject. Unfortunately, the book does not keep up with the fast-paced changes of the past several years, including the mounting evidence for cosmic acceleration and a cosmological constant. But then, there are *Scientific American* articles for that.

BRENDA FOWLER'S *Iceman: Uncovering the Life and Times of a Prehistoric Man Found in an Alpine Glacier*. Random House, New York, 2000 (\$25).

A German couple hiking in Austria's Ötztal Alps in 1991 found a well-preserved body melting out of a glacier. With the remains were a flint-blade dagger, an ax with a copper blade, an unfinished longbow, a quiver with two finished and 12 unfinished arrows, and a pair of birch-bark containers. Ötzi, as the Austrians named him, was a figure from an ancient past—some 5,300 years ago, according to radiocarbon dating. He provided science with a rare opportunity to assemble information about little-known aspects of Neolithic life. Journalist Fowler describes the findings with care.

Alas, the Iceman also provided the occasion for a remarkable amount of bickering. The Austrians thought he was theirs, but a survey showed that he lay in what is now Italy, just 101 yards south of the border with Austria, and so he is now on display at a new museum in Italy's South Tyrol. Additional quarrels arose over the manner of preserving the body, the money to be paid for and made from the discovery, and the conflicting scenarios of how the Iceman met his end. Fowler sets all that out, too. She makes an absorbing story of the saga.



FROM ICEMAN

PETER MATTHIESSEN'S *Tigers in the Snow*. Introduction and photographs by Maurice Hornocker. North Point Press, a division of Farrar, Straus & Giroux, New York, 1999 (\$27).

Hunting and loss of habitat reduced the world's tiger population from about 100,000 at the beginning of the 20th century to around 5,000 at the end of it. At least three of the eight species of *Panthera tigris* are effectively extinct in the wild. And although the tiger "rivals the African elephant and the blue whale as the most majestic and emblematic creature," its ways are little known "because of its crepuscular and covert habits." Matthiessen, in his 19th nonfiction book, tells the sad tale of the tigers. He treats in particular *P. t. altaica*, the Siberian or Amur tiger. Hunted almost to extinction, it began a recovery after the Soviet Union established in 1936 the Sikhote-Alin Reserve some 300 miles northeast of Vladivostok. But with the collapse of the Soviet Union, the tiger has come under siege again.

Matthiessen describes a countervailing effort, the Siberian Tiger Project. It is a Russian-American research venture established in 1992 to study the creature's habits in order to provide a strong scientific base for recommendations to government authorities on how to save the tigers. Will they survive? Maybe not, with global corporations moving to exploit the Russian Far East. Says Matthiessen: "Without intervention and protection (while the businessmen come to their senses), efforts to save rare species such as the Amur tiger and the Far Eastern leopard will be in vain."



FROM *TIGERS IN THE SNOW*

J. CRAIG WHEELER'S *Cosmic Catastrophes: Supernovae, Gamma-Ray Bursts, and Adventures in Hyperspace*. Cambridge University Press, Cambridge, England, 2000 (\$24.95).

For 25 years, Wheeler, a professor of astronomy at the University of Texas at Austin, has taught a course called Astronomy Bizarre. Its aim is "to introduce some of the exotica of astronomy for which one has little time in the standard introductory course for non-science majors." Exotica, indeed, populate this book that derives from the course. Accretion disks, supernovae, neutron stars, black holes and gamma-ray bursts march through, all presented with a clarity that doubtless comes from Wheeler's long experience in teaching astrophysics to "bright, interested, but nontechnically trained students." And then he gets to what might be called superexotica: wormholes, time machines, quantum gravity and string theory. It is heady stuff, as he says. So is what he calls "the deepest issue that drives both physicists and theologians." It is, "Why are we here?"

BOBBI S. LOW'S *Why Sex Matters: A Darwinian Look at Human Behavior*. Princeton University Press, Princeton, N.J., 2000 (\$29.95).

Sex differences, Low says, are central to our lives. Are they genetically programmed or the result of social traditions? "New research ... supports the perhaps unsettling view that men and women have indeed evolved to behave differently." The differences arise from "the fundamental principle of evolutionary biology, that all living organisms have evolved to seek and use resources to enhance their reproductive success." Low, a professor of resource ecology at the University of Michigan, develops her argument through examinations of genetics, primate societies, and human behavior past and present. Then she asks a haunting ques-

tion. Have we, simply by doing well what we have evolved to do, "changed the rules so that now it may even be detrimental to 'strive' to our utmost abilities?" It seems likely, she says, "that we will face new problems as growing, and increasingly consumptive, human populations interact with environmental ... stability."

J. L. HEILBRON'S *The Sun in the Church: Cathedrals as Solar Observatories*. Harvard University Press, Cambridge, Mass., 1999 (\$35).

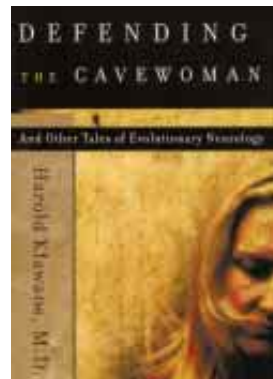
"The Roman Catholic Church gave more financial and social support to the study of astronomy for over six centuries ... than any other, and, probably, all other, institutions," Heilbron writes. "Those who infer the Church's attitude from its persecution of Galileo may be reassured to know that the basis of its generosity to astronomy was not a love of science but a problem in administration. The problem was establishing and promulgating the date of Easter." And the key to that was establishing the time of the sun's return to the same equinox. "The most powerful way of measuring this cycle was to lay out a 'meridian line' from south to north in a large dark building with a hole in its roof and observe how long the sun's noon image took to return to the same spot on the line." That is how several cathedrals became solar observatories. Heilbron focuses on four of them—San Petronio in Bologna, Santa Maria degli Angeli in Rome, Saint Sulpice in Paris and Santa Maria del Fiore in Florence. He also describes meridian lines in a number of other buildings.

Heilbron is a historian, formerly a professor of history and vice chancellor at the University of California at Berkeley and now senior research fellow at Worcester College of the University of Oxford. He has researched his subject deeply, with the result that he presents a rich history of early astronomy, the development of the calendar and the relations between the Church and science.

HAROLD KLAWANS'S *Defending the Cavewoman: And Other Tales of Evolutionary Neurology*. W. W. Norton & Company, New York, 2000 (\$24.95).

If it weren't for the cavewomen, Klawans maintains, men would still be chipping flints and hunting with spears. "Our advantages over other species are most probably due to the development of a complex language," he writes. "And women are far more likely to have played the more significant role in this than men." So, "over a million years or two, the result was the evolution of brains selected for acquisition of language and other skills during the period of prolonged juvenilization."

Klawans, a neurologist, was interested in the evolved brain and the things that sometimes go wrong with it. Among the intriguing cases he describes—all involving people he had treated or seen—are those of a professor of English who picked up his newspaper one morning and found that he could no longer read, a welder who developed symptoms resembling Parkinson's disease after years of welding with rods containing manganese, and an Italian conductor who could lead an orchestra brilliantly even though a stroke had cost him his ability to speak and understand speech. Klawans relates his tales well, easily conveying a great deal of information about evolution, the brain and dealing with brain disorders.





Time Exposures

All photography needs time to collect an image, muse **Philip & Phylis Morrison**, and over very long times, nearly invisible marvels can appear

A little group of science teachers, none of them with more than point-and-shoot photographic experience, had built a pinhole camera and were impatiently awaiting their first picture through the long minutes of time exposure. But when they saw the faithful image of the scene, it came as a surprise to all the experimenters. Although one person had reached into the middle of the view to make an adjustment there during the exposure (and all agreed they had seen it happen), there was no sign of it in the final composition. Somehow the camera had edited out the intruder, without losing any of what must have been hidden! For a while it seemed magical.

The pinhole camera required minutes of exposure to make its image, but *taking a picture* still seemed to these experimenters a single act, one not to be divided into parts. If you were in the picture, there you must appear. The real physical process had been subsumed into a single moment. Of course, the few seconds of intrusion meant that only a small fraction of the light energy that had formed the rest of the image was there to capture the vagrant arm, not enough for a noticeable record. No image is an instantaneous act; time exposures are all we ever see, short or long, and none will visibly report too brief a presence. Only the in-built photochemistry of suntanned skin provides a familiar long exposure: no snapshot of a passerby was ever caught via a suntan!

The story suggested to us that we should assemble a few examples in which a long time spent in imaging was essential. The first of all photographic scenes able to endure ambient light without fading was made in 1826 by a French experimenter, Nicéphore Niepce. His pioneer image was formed in a layer of varnish that incorporated a special powdered pitch that hardened on exposure to light. The dark, softer parts were dissolved away on "developing" the image with a slow solvent; the remaining harder parts reflected light well. Niepce had aimed into the small court-

yard below his apartment. Begun in the morning, that first exposure lasted eight hours, enough for the sun to pass well across the sky. Sunbeams caught first one and then the opposite wall of the small courtyard, surprisingly sunlit together in the image. Niepce soon joined his efforts with Louis Daguerre, whose much better, if still very slow, daguerrotype process was a success for decades, preserving images on slips of metallic silver, presaging the silver halide techniques that are still the basis of film photography.

The deepest images we now have of the extragalactic past are long time exposures made by the Hubble Space Telescope. There are two Hubble Deep Fields: one clear, dark field taken looking northward from the Milky Way in 1995, the other southward in 1998. The 94-inch telescope in Earth orbit radios its digital images down, reading out the photoelectrons generated in millions of silicon pixels in its focal plane, a grand video camera aloft. (The color posters derived from those images, each with about 1,500 galaxies in a small field, are to be admired on many a wall.) The Hubble, after its first vital repair, stands as a tribute to the virtues of a design and service plan that foresaw repeated maintenance visits by shuttle-borne astronauts of consummate skill and evident courage.

The telescope needs dark skies, of course; Earth's shadow of nightfall enfolds it about every 90 minutes. The time exposures meant taking several dark-sky images of one small spot, each shot well guided, then superposing them with monitored precision. The longest single exposure of the many that built up the Southern Deep Field was 2,700 seconds. Comparable exposures when added to-

gether catch enough photons to form the four-color image of all intervening optical sources out to a distance of a dozen billion light-years. Some 200 to 400 pictures of varying quality contributed to each Deep Field. The 100-hour exposure summed up during 10 consecutive days in orbit is not sufficient to record for certain even a few photons from individual stars like the sun out near the depth limit. The images show only a chance fraction of the stars that superimpose to build galaxy images, now under eager study; a



few among them are seen posing nearby in their maturity, but many more are very far away and still caught in youth.

Another time exposure that is all but whimsical in its simplicity touched deeper issues than any other. It was reported early in 1909 by a University of Cambridge graduate student, Geoffrey I. Taylor, who was not quite 23 years old. He carried out with flair the suggestion of his eminent supervisor, Sir J. J. Thomson. Could the photons described by young Albert Einstein's first 1905 paper as indivisible bundles of light energy generate the elegant diffraction patterns so perfectly described by the wave theory? Very feeble light, photons coming one by one, might make no clear patterns, even if a

Continued on page 111

Not What It Seems

James Burke explores crystals, sheepish matters, monster chicks, poets and other smoke-and-mirrors stuff



DAVE PAGE

When the humongous French storms of last December knocked bits off the great medieval Cathedral of Notre Dame de Paris, I wasn't quite as put out as might have been expected. As you will soon see, I had my reasons.

All those pieces of broken gargoyle smashing on the ground brought to mind Notre Dame's own great smasher, René Just Haüy. Who spent his life smashing crystals, pretty much inventing the modern lattice theory of crystal formation and being hot stuff on pyroelectricity. And because Haüy was priest as well as scientist, Napoleon gave him a freebie post as honorary canon of Notre Dame, in return for turning out a physics textbook for the new French school system. Haüy had started out as a botanist but went mineralogical as a result of attending the lectures of Louis Jean Marie Daubenton, who was, among other things, a tour guide at the Jardin des Plantes in Paris and who first made his scientific name with a paper (doubtless well received by his gastronome superiors) on a method for classifying shellfish.

Daubenton also kind of invented comparative anatomy for fossils, investigated palm-tree trunk growth, and became France's leading expert on merino wool and anything reproductive you might ever want to do with rams and ewes. Under the revolutionaries, in 1793, this earned him a certificate of good citizenship, in which he is described as "shepherd." You get a feel for the man from the fact that he referred to the odd moments when he turned to fiction as putting his mind "on a diet."

Daubenton's assistant was Étienne Geoffroy Saint-Hilaire, professor of quadrupeds, cetaceans, birds, reptiles and fish, who in the end went a little weird. But meantime, in 1821, he pub-

lished the nifty (almost evolutionary) theory that species could change and take on forms that hadn't been in the Great Original Plan, on those rare occasions when nature happened to make a mistake (a.k.a. a deviation from the G.O.P.) and generated a monster (a.k.a. a new species). His paper, "An Essay on the Classification of Monsters," pretty much kicked off the science of teratology (the study of malformation).

Some would say he got these monstrous ideas (which I suppose helped pave the way for Darwin) from the first proper study of malformation by well-heeled 17th-century English big cheese William Harvey, physician to

movers and shakers ("Brief Lives") is that you couldn't trust a word of gossip he wrote. He got away with it all because he had a protector with friends in high (read: royal) places: Sir William Petty, the political economist who spelled out the balance-of-trade idea and co-authored the first book on statistics. And who was so shortsighted that on one occasion when challenged to a duel, and therefore given the choice of weapons and venue, said: "Axes, in a dark cellar." The other guy withdrew.

Early in life, as a boy sailor, Petty was so disliked by one crew that they marooned him on the coast of France.

William Harvey thought **the blood carried the soul** and heat and that the blood got hot by fermenting in the heart.

the king. A man obsessed by the chick-and-egg problem of hens and their output. Harvey is also the guy who we're told made medical history with his 1628 publication on the circulation of the blood. I enjoy what they don't usually tell you: that he thought the blood carried the soul and heat and that the blood got hot by fermenting in the heart.

Unfortunately for Harvey, one of the penalties of being rich and famous in 17th-century England was that you got yourself written up by someone the contemporary equivalent of Dorothy Parker: a pen dipped in acid, but you couldn't help enjoying the bons mots (unless they were about *you*). This creep was John Aubrey, who spent much of his life surveying bits of England and running away from litigious women. About the best anybody says about his essays on

So he stayed on, got a French education and ended up in Paris hobnobbing with the Gallic eggheads at the salon of Father Mersenne, who put so many scientists in touch with one another that he was networking before it had a name. Mersenne found time for a little research, too: in acoustics, figuring out that the intensity of a sound was inversely proportional to the distance from its source.

In 1754 an Italian music teacher, Giuseppe Tartini, discovered that two notes played simultaneously and with intensity created a third note. He also produced what have been described as "seriously inaccurate" calculations applying algebra and geometry to music. But he ran one of the best violin-playing schools in Italy, where he introduced the modern style of bowing. Which lacked only the modern style of bow, developed around 1786 in Paris by François Tourte at a time when per-



formers and composers wanted a better bow, to make more expressive noises. Three years later seven-year-old Niccolò Paganini took his first bow in a career that did more for expressive noises than ever before—and perhaps since. The critics ran out of superlatives for Paganini, who kind of invented virtuosity. Sometimes for fun he'd cut two strings on his fiddle and finish the piece perfectly on the remaining two.

And in the vein of "it takes one to know one," he dumped a fortune on Hector Berlioz so that the composer could afford to express his genius (despite the total indifference of the Paris critics) and feed his wife, a second-rate English actress named Harriet Smithson. Like Berlioz, she got nothing but lousy reviews. Except for a few kind words from one of her husband's librettists, the poet Théophile Gautier, who had his own peculiarly French domestic financial responsibilities: two sisters, three children and two mistresses.

Gautier was highly regarded by fellow scribblers for his art-for-art's-sake, only-beauty-is-sovereign views of life, his poetry (okay if you like something that feels like the *n*th work-over), and his lit crit (required reading for salon-goers). By this time (1840), however, Gautier et al. were off that particular cocktail circuit and into deeply meaningful sessions at Victor Hugo's, where Romantics talked *about* themselves *to* themselves.

One fellow narcissist on these occasions was Prosper Mérimée, whom I have mentioned and who, besides writing novels about the past, was the French Inspector General of the Past (that is, Historical Monuments). Major mission: shoring up what was falling down. Most of the actual repair work was done by his protégé, whose later ideas about using iron structures with nonload-bearing masonry walls went over very big in Chicago and helped those shaping the American cityscape, skyscraper-wise: namely, architect Eugène-Emmanuel Viollet-le-Duc. The Dook (my sobriquet) wrote no fewer than 16 volumes on the history of French architecture and was nuts for *le gothique*. So nuts that when he approached a suitable case for restoration, what he didn't like (or what was missing) he reinvented from his fertile, Disney-like imagination. Which is why so much of so many of his restored ancient French buildings is fake.

Including large chunks of the big one whose damage I began by not lamenting, because some of the medieval stuff that hit the ground last December ... wasn't. SA

Wonders, continued from page 109

long exposure ensured enough total light energy to record well.

Taylor set his apparatus up at home; it cost him a pound sterling. A small, steady gas flame was his light source, reduced in intensity by filters that were homemade soot-smoked glass slides. He calibrated each filter by timing the exposure required to match the blackness of a negative made directly with the full light of the flame. For the experiment he set up a narrow slit to define the beam, and a needle beyond the slit to cast its shadow and the interference fringes around it on the plate. The darkest of four filters extended the exposure needed to reach adequate blackness to three months' time!

The diffraction pattern was present. "In no case was there any diminution in the sharpness of the pattern," Taylor wrote. By comparison with a standard candle, he could estimate the energy density of the visible light that passed his darkest filter as about that of a candle two miles away, one photon entering the pattern volume every 10th of a second on average. Each photon reached the plate from the slit in a matter of nanoseconds, so that nearly all the 100 million

photons came to the plate one at a time. This student's simple time exposure probed the depth of quantum physics.

Once before, after Thomas Young's slit patterns of 1801, Newton's light particles lost all credibility for a century to the wave theory. Quantum electrodynamics gave us our present picture in the 1930s: it says that the electromagnetic patterns are fully present in space just as James Clerk Maxwell's equations describe but that the energy of each photon is delivered to individual atoms only statistically, under odds determined by the pattern as a whole. These ideas have remained, subtle but well tested, for more than 70 years.

Sir Geoffrey Taylor of Cambridge would become a celebrated leader in classical mechanics in his remarkably long and productive life. He went a long way toward explaining cracks in crystals, blast waves, turbulence—even just how water pours out of an inverted tumbler. A keen yachtsman, he recalled quite credibly that during those long 1909 exposures, he had gone sailing. We find no remarks by the early quantum masters, such as Max Planck and Einstein, to suggest that they had ever heard of Taylor's fundamental demonstration. SA

COMING IN THE AUGUST ISSUE OF SCIENTIFIC AMERICAN

IS GLOBAL WARMING
**HARMFUL TO
YOUR HEALTH?**



JETS AND DISKS AROUND STARS

ON SALE JULY 27

SHENG UNEP/Still Pictures/Peter Arnold, Inc.; NASA



Alcohol, Tobacco and Soy Alarms

Analysis of large numbers of people can turn up some surprising insights about the things we put in our mouths, notes **Steve Mirsky**

Epidemiologists are the unsung heroes of medicine. Emergency room physicians and their co-workers garner the good press and get entire television series devoted to their exploits. The attention is richly deserved, because they perform truly gallant labors. But the hard fact is that the ER docs save lives one at a time. Epidemiologists, through their analyses of the health and habits of big groups of people, save lives wholesale.

The other hard facts are (a) a TV show about epidemiologists would be about as exciting as vanilla ice cream, not to mention that this particular vanilla ice cream wouldn't get eaten because of epidemiological studies showing the dangers of high-fat diets, and (b) epidemiologists

drive us crazy. Is margarine better than butter? This week, possibly; tune in next week for the latest exciting findings.

This past April saw a small shower of epidemiological publications that made the eyes glaze and the head spin, which anecdotal evidence associates with dizziness or demonic possession.

Item: Tofu or not tofu? The bland bastion of vegetarianism, tofu got its first bad press outside of a restaurant review. A study in the April issue of the *Journal of the American College of Nutrition* noted a connection between tofu consumption during middle age with cognitive impairment in later years. The data lead to the chilling conclusion that eating lots of tofu is correlated with losing the equivalent of three years of education. In other

words, if you ate tofu twice a week all through junior high school you were just about breaking even. Can't recall who wrote the Federalist Papers? Maybe tofu's to blame. Think that Calculus is the hero of the movie *Gladiator*? Tofu may be the culprit. Not sure what the heck tofu is? Might be the tofu. (Decreased rates of cancer and heart disease? Also might be the tofu.)

Item: Cigarettes fail to fend off the tofu effect. A few small studies had intimated that smoking might protect against Alzheimer's disease and other forms of dementia, probably thanks to the nicotine. But research involving more than 34,000 men, published in the April 22 issue of the *British Medical*

Journal, found no brain-preserving effect from cigarettes. The *BMJ* paper thus grabs medicinal smokers by the lapels and says, "Wise up." (The authors include Richard Doll and Richard Peto—these guys are just about the most famous epidemiologists out there, if such a description isn't oxymoronic.)

Item: Beer is really good for you, so maybe they can sell it in the part of the health food store formerly reserved for tofu. Red wine gets most of the health praise reserved for adult beverages, but a study in the April 29 issue of the *Lancet* finds that beer may be even better. All alcohol raises levels of homocysteine, and that's bad, as homocysteine is associated with heart disease and counters some of alcohol's good intentions. But beer also includes pyridoxine, and that's good, because it keeps homocysteine levels down. Pyridoxine is more commonly known as vitamin B₆, which will henceforth be less commonly known as B_{6-pack}.

Item: Beer is really bad for you, in ways you probably couldn't imagine. A study in the April 28 issue of the *Morbidity and Mortality Weekly Report*, published by the Centers for Disease Control and Prevention, concludes that cheap beer leads to gonorrhea. The relation presumably results from the powers of beer to get young adults to engage in risky behaviors, such as driving or other things you can do in a car. The authors estimate that a 20-cent tax hike per six-pack should lower national rates of gonorrhea by almost 9 percent, apparently by forcing some people to keep their hands in their own, empty pockets.

In conclusion, then, epidemiological studies prove that smoking totally stinks and that the old adage should now read: Eat (but be careful of tofu despite its many other probable health benefits), drink (but make it a beer and please be willing to pay a little more for it for the benefit of society as a whole) and be merry. Which has no downside. Yet.

